Neuronal Stem Cell-Drug Interactions: A systematic Review and Meta-Analysis

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Running Head: Neuronal Stem Cell-Drug Interactions

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Disclaimers

None.

Acknowledgements of Grants

M.I. was supported by a scholarship from the Indonesia Endowment Fund for Education from Indonesia's Ministry of Finance (Award number: S-2257/LPDP.3/2016).

Key Words: stem cells; nervous system; drug interactions; comorbidity; systematic review; meta-analysis

Abstract

Objective: Stem cell therapy is a promising treatment option for neurodegenerative diseases that mostly affect geriatric patients who often suffer from comorbidities requiring multiple medications. However, not much is known about the interactions between stem cells and drugs. Here, we focus on the potential interactions between drugs used to treat the comorbidities or sequelae of neurodegenerative diseases and neuronal stem cells, to reveal potential effects on drug safety and efficacy.

Methods: To determine the potential effects of drugs frequently used in geriatric patients (analgesic, antibiotic, antidepressant, antidiabetic, antihyperlipidemic, and antihypertensive drugs) on neuronal stem cell differentiation and proliferation, we systematically searched PUBMED to identify non-review articles published in English in peer-reviewed journals between January 1, 1991 and June 7, 2018.

Results: We identified 5,954 publications, of which 214 were included. Only 62 publications provided complete datasets required for meta-analysis. We found that antidepressants stimulated neuronal stem cell proliferation but not differentiation under physiologic conditions and increased the proliferation of stem cells in the context of stress. Several other potential interactions were identified, but the limited number of available datasets precludes robust conclusions.

Conclusions: Although available data were in most cases insufficient to perform robust meta-analysis, a clear interaction between antidepressants and neuronal stem cells was identified. We reveal potential other interactions requiring further experimental investigation. We recommend that future research addresses such interactions and investigates the best combination of pharmacological interventions and neuronal stem cell treatments for more efficient and safer patient care.

Significance Statement

Since drugs frequently used in geriatric patients can influence the behavior of neuronal stem cells, which are a promising therapeutic option for the treatment of neurodegenerative diseases, our study aimed to identify potential interactions between neuronal stem cells and drugs described in the literature. Although only surprisingly few studies reported data on such effects, meta-analysis revealed a clear interaction between antidepressants and the proliferation capacity of neuronal stem cells. Therefore, both future cell therapeutic approaches and pharmacological interventions need to be coordinated thoroughly to create more efficient, safer, and ultimately successful therapeutic strategies.

Introduction

Aging is the main risk factor for neurodegenerative diseases.[1] More than 20 percent of adults at the age of 60+ years suffer from mental or neurological disorders. This number is expected to double in individuals of over 70 years.[2, 3] In addition, there has been a tremendous rise in the number of geriatric patients suffering from mental or neurological disorders during the last decade, which is even expected to increase as our population ages.[4] Unfortunately, conventional pharmaceutical interventions for neurodegenerative diseases are often limited in efficacy.[5-9] This has encouraged the search for alternative therapeutic approaches, with neuronal stem cell therapies being among the most promising options.[10] Although clinical translation has not yet been achieved, numerous preclinical studies using neuronal stem cells provided encouraging results.[10-13]

Geriatric patients are the primary patient population to benefit from prospective stem cell-based approaches to counter neurodegenerative diseases. As older people often suffer from several chronic diseases, including hypertension, diabetes, chronic pain, or depression,[14] it is relevant to consider the prevalence of polypharmacy in the target patient population.[15] The primary challenge of the inevitable combination of neuronal stem cells and drugs in clinical practice is to yield beneficial, potentially synergistic effects while avoiding detrimental ones. Therefore, a deeper understanding of the functional mechanisms of each drug and their interactions with neuronal stem cells is an important prerequisite for successful combination therapies.[16] While this aspect has not been systematically investigated for neuronal stem cells, research in the cardiac field indicates the existence of such interactions and their considerable complexity.[17]

In this study, we hypothesized that there are interactions between neuronal stem cells and drugs frequently used in geriatric patients. We intentionally choose the term “neuronal stem cells” to distinguish it from “neural stem cells”, which can differentiate into neuron and glia, since neurons are the primary focus of stem cell therapy in the brain. We performed a

systematic review to identify (i) the effects of drugs on neuronal stem cell proliferation and differentiation, (ii) potential differences in exerting those interactions according to drug classes, subclasses or particular drugs, and (iii) the mechanisms underlying drug-stem cell interactions.

Methods

We conducted a systematic review according to the guidelines for Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[18]

Search Strategy and Selection Criteria

We searched for publications listed in PUBMED describing the effect of drugs frequently used in geriatric patients on neuronal stem cells. A detailed search query is provided in the **Supplemental Data**. Publications made between January 1, 1991 and June 7, 2018 were included. We chose the start date based on when stem cells started to become widely explored as potential therapeutics. Data from pathological cells (e.g., tumor cell lines) and non-mammalian species were excluded. We included *in vitro* and *in vivo* studies as well as clinical trials of the peripheral and central nervous system (including the retina). Only publications in peer-reviewed journals containing primary data were used for analysis. Review articles, articles without full text accessibility, and non-English articles were excluded.

Selection of Publications and Data Extraction

One author (M.I.) screened the abstracts and all authors subsequently reviewed the full-text versions of the potentially eligible publications. In case of doubt, publications were discussed in consensus meetings with two other authors (M.Z. and J.B.). After screening, a quality synthesis was performed. It included all aspects referring to the internal validity of the publications, such as reporting of outliers, technical or biological replicates, and blind

assessment of outcome. The distribution of drugs, samples, and the effect of the drugs on the outcome parameters were determined. Where data were stated in the text, numerical values were extracted. When a study reported several experiments, each experiment was considered as an independent experiment. Only the concentration of the drug exerting the largest effect on the stem cells and the final time point of the experiment were included in the dataset.

We discriminated three distinct conditions under which the data were gathered: 1) "physiologic", in which the physiological state of neuronal stem cells was investigated, without any modification of the cells or animals during the experiment, 2) "injury" (including mental disorders), where the sample a) mimicked a phenotype of disease (as disease models) or b) received a psychological challenge such as depression or a harmful or negative physical stimulus (e.g., pain), and 3) "modified", in which the animals were either genetically modified (transgenic), were housed in an enriched environment, or exposed to a combination of drugs. We identified proliferation by bromodeoxyuridine (BrdU), Ki67, 3H-Thymidine, 5-Iodo-2-deoxyuridine (IdU) staining and differentiation by detection of doublecortin (DCX), neuronal nuclei (NeuN), neuron-specific class III beta-tubulin (TUJ-1), ionized calcium-binding adaptor molecule 1 (Iba-1), nestin, glial fibrillary acidic protein (GFAP), microtubule-associated protein 2 (MAP2), or beta-III tubulin.

For meta-analysis, two authors (M.I. and A.P.) independently extracted the relevant data from the included publications. We collected data on sample size, mean, standard deviation, p-value, statistical analysis, and the reported mechanism underlying the action of the drugs on neuronal stem cells. We contacted the authors of the publications that did not provide the complete dataset to collect the missing information. In case the data were only available as graphs, we performed graphical measurement using ImageJ (version 1.51S, RRID:SCR_003070) as previously described to calculate the mean and standard deviation.[19]

Statistical Analysis

To compare data from the different publications, we used the standardized mean difference (SMD) since the measurement units of proliferation and differentiation were very diverse among the publications. Hedge's g SMD with correction factor was chosen due to the small sample size (below 20 samples for each study). We applied partitioning of heterogeneity to determine the significance of reported study quality explaining differences in observed efficacy. We calculated an estimate of the effect size based on the visual assessment of the forest plot and I^2 value by the DerSimonian and Laird random effect model meta-analysis. A confidence interval of 95% was applied. We generated the analyses using Cochrane's Review Manager Software for meta-analysis (*RevMan* Version 5.3, RRID:SCR_003581) as well as manually in Excel as previously reported.[20] An exemplary calculation can be found in the **Supplemental Data** and the complete Excel calculation sheet in the **Supplemental xls**. A probability value of $p<0.05$ was considered statistically significant, except for the subgroup analysis where the obtained p-values were compared to the Holm-Bonferroni cutoff p-value to correct for multiplicity.[21] The Holm-Bonferroni cutoff p-value is calculated as follows: (target α (=0.05)) / (k – rank number of pair (by degree of significance) + 1), where k is the number of tests.

Results

After the screening of 5,954 publications, we identified 214 eligible publications, of which 115 were records in the physiologic, 69 records in the injury, and 32 records in the modified condition (**Figure 1, Supplemental Table 1**). The distribution of drug classes, subclasses and individual drugs among all conditions produced some predominant clusters especially for antidepressants and analgesics (83 and 40 number of records, respectively; **Table 1 and 2**). The records in the injury (including mental disorders) and modified conditions were very heterogeneous (**Supplemental Table 2**). Among all conditions, we found that more than two thirds of the publications (148 of 214 publications, 69.2%) used hippocampal stem

cells, but no record reported that neuronal stem cells were transplanted into an animal model or patient while assessing the effect of drugs used in geriatric patients on neuronal stem cells (**Supplemental Table 3**).

Drug Effects on Neuronal Stem Cells

Table 3 shows the number of publications reporting stimulating, neutral, and inhibiting effects on proliferation and differentiation of neuronal stem cells for each drug class summarizing all conditions. **Supplemental Table 4** presents equivalent information only under physiologic conditions. Antidepressants had a predominantly stimulating effect on neuronal stem cell proliferation and differentiation while analgesics showed the opposite effect in all conditions. Similar findings were obtained when looking at the physiologic condition alone. For the other drug classes, no predominant effect was observed (**Table 3, Supplemental Table 4)**.

We further divided the drug classes into different subclasses and individual drugs to identify differences within a drug class. However, neither specific drugs nor subclasses mediate different effects compared to the main drug classes (compare **Table 3** with **Supplemental Table 5**).

Meta-Analysis

Statistical data such as sample size, mean, and standard deviation are required to perform meta-analysis. Overall, we identified 61 datasets reporting complete information. First, we extracted 42 complete datasets from the publications. Second, we obtained 19 additional datasets after contacting the authors of the publications that do not contain all of the aforementioned data (we only contacted the authors when 5 or more records were available per condition and drug class, our predefined threshold to perform meta-analysis). Third, we measured the mean and standard deviation directly from the respective graphs of 24 additional

publications. Those only stated the sample size and their authors did not respond to inquiries. With all other datasets, at least one parameter was missing to calculate the effect size.

Only the data of the antidepressant drug class were sufficient for meta-analysis, of which 21 records described the effect on proliferation and 7 on differentiation in the physiologic condition, while 6 records were on proliferation in the depression condition (**Supplemental Table 6-8**). Meta-analysis confirmed that antidepressants significantly stimulated neuronal stem cell proliferation in the physiologic condition (Hedges' g SMD, 0.66; 95% CI, 0.20 to 1.12; p=0.005, **Figure 2A**). The most frequently studied antidepressant subclass, selective serotonin reuptake inhibitors (SSRIs, **Table 2**), also significantly induced proliferation of neuronal stem cells (Hedges' g SMD, 0.72; 95% CI, 0.17 to 1.27; p=0.01 <0.017 (Holm-Bonferroni cutoff p-value), **Figure 2A**). We also performed meta-analysis on the effect of antidepressants on neuronal stem cell differentiation, which was not significantly changed (Hedges' g SMD, 0.23; 95% CI, -0.68 to 1.13; p=0.63, **Figure 2B**). Furthermore, there was no statistically significant evidence that antidepressants stimulate stem cell proliferation in models of depression (Hedges' g SMD, 1.14; 95% CI, -0.03 to 2.32; p=0.06, **Figure 3**).

Potential Effect of Drugs on Neuronal Stem Cells in the Context of Brain Injury

Some publications offer insights into the potential effect of drugs on neuronal stem cells in the context of brain injury that may be informative for future research. We found 20 records investigating drug-stem cell interactions in *in vivo* and *in vitro* models of brain ischemia and hypoxia. For instance, the phosphodiesterase type-5 inhibitor sildenafil stimulated proliferation of neuronal stem cells (5 records). We cannot exclude that the injury condition itself influences drug-stem cell interactions, but in the case of sildenafil, the stimulating effect on neuronal stem cell proliferation was also found under physiologic conditions. However, the overall number of publications with complete datasets and the

heterogeneous effects were too low to perform robust meta-analysis in the brain injury subgroup.

Discussion

Our systematic review revealed that the effects of drugs used in geriatric patients on neuronal stem cells have not been studied in much detail so far. In fact, the identified publications reported such interactions as an auxiliary finding. Relatively few publications exist on a limited number of drugs, and their heterogeneity was high with respect to the type of experiment (*in vivo* or *in vitro*), condition under which the drugs were assessed (physiologic, injury or modified) and the investigated drugs (**Table 1 and 2, Supplemental Table 2 and 3**). We intentionally chose to investigate neuronal stem cells in their various types and applications because we wanted to provide a comprehensive overview about the interactions of neuronal stem cells and drugs *in vitro*, *in vivo,* and in clinical trials. We found that, although there are numerous studies using *in vitro* and *in vivo* models, there is no clinical trial investigating drug-stem cell interactions. In addition, we only found studies in cultured neuronal stem cells or endogenous stem cell populations *in vivo* (**Supplemental Table 3**). In those studies that investigated transplanted cells, only mesenchymal stem cells, but not neuronal stem cells were used.[22]

Nevertheless, we were able to show a clear interaction between antidepressants and neuronal stem cells in the physiologic condition and in models of depression (**Figure 2 and 3**). The results obtained by studies using well-suited animal models may be relevant for clinical treatment. Antidepressants may serve as an example: In case their class effects on proliferation and differentiation of neuronal stem cells was proven for particular antidepressants, those may be considered as the treatment of choice for post-stroke depression even in case alternative drugs may provide better primary anti-depressant effects, but less regenerative stimuli. However, the situation may be far more complex in human patients. It is important to

understand that proliferation and differentiation were chosen as the pre-set criteria for stem cell function in our analysis. Although important for stem cell function, these parameters are neither the only ones indicating improved functional recovery after stroke, nor the most important ones. This is underlined by the recently published, neutral results of the Fluoxetine Or Control Under Supervision (FOCUS) trial study.[39] While fluoxetine was effective in preventing post-stroke depression, there were no obvious effects of functional recovery, but a higher rate of bone fractures as an adverse event.[23]

Further investigations regarding the modes of action of the drugs revealed functional hypotheses for pathways underlying their effects on neuronal stem cell differentiation and proliferation (**Figure 4**). Verifying those and elucidating the underlying mechanisms is an important step to develop more effective and specific drug-stem cell combination treatments and to minimize potential adverse effects.

Potential Mechanisms Affecting Proliferation and Differentiation

In order to understand the drug effects on neuronal stem cells, we also assessed the underlying mechanisms investigated in the included publications. Among all records in the physiologic condition, the six most frequently utilized drugs (fluoxetine, imipramine, morphine, rosiglitazone, rapamycin, and insulin, **Table 2**) have been tested for their mechanism of action. However, the identified pathways were only described in a single publication each (**Figure 4**) and therefore still need to be verified:

Fluoxetine, imipramine, and morphine affect the mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) pathway.[24-26] This is one of the key signaling pathways modulating neuronal stem cell proliferation and differentiation.[27] MAPK signaling contributes to synaptic plasticity and long-term memory formation.[28] It is also supposed to be neuroprotective.[29]

The antidepressant fluoxetine increased proliferation of neuronal stem cells. This is likely mediated by activation of serotonin-1-agonist receptor (SHT1Ar, **Figure 4**).[30, 31] SHT1Ar activates phosphatidylinositol-4,5-biphosphate 3-kinase (PI3K), followed by an increase of Akt1 that in turn increases neuronal stem cell proliferation.[32] Moreover, SHT1Ar triggers the MAPK/ERK cascade which increases neurogenesis by stimulating cyclin D1.[30] Hui and colleagues reported that SHT1Ar induces ser9, which inhibits glycogen synthase kinase 3β (GSK3ß) followed by activation of β-catenin.[31] Another potential mechanism is that SHT1Ar stimulates the cAMP response element-binding (CREB) protein by activating MAPK/ERK.[24] In a study unrelated to SHT1Ar, fluoxetine stimulated cyclin-dependent kinase (CDK) inhibitor protein 1 (P21/CIP1) leading to increased neurogenesis.[33]

Rapamycin and insulin affect the mammalian target of rapamycin (mTOR) signaling pathway in different ways. Insulin stimulates mTOR and rapamycin inhibits it.[34, 35] mTOR is a receptor tyrosine kinase that is pivotal in regulating cell proliferation and differentiation.[36] Inhibition of mTOR blocks p70 ribosomal S6 Kinase (S6K) which then leads to the inhibition of stem cell differentiation via telomerase activity reduction.[35, 37] S6K has been well-known in regulating the cell cycle, growth, and survival.[38]

An antidiabetic drug from the subclass of thiazolidinediones, rosiglitazone, stimulates the neurotrophic factor α1 (NF-α1) which then upregulates the fibroblast growth factor-2 (FGF-2). FGF-2 induces neurogenesis in the hippocampus.[39] Another study demonstrated that FGF-2 needs cystatin C to induce its mitogenic activity.[40] Unfortunately, this was not confirmed by the identified publications.

Altogether, the pathways described to be influenced by the drugs in the identified publications fit to the results of other publications on neuronal stem cell proliferation and differentiation. However, although they are potential therapeutic targets, these pathways also control many very fundamental cell processes. Modulating these pathways may therefore cause interference with important basic cellular functions. Hence, it would be necessary to find more

specific targets avoiding adverse side effects and/or supporting positive effects. In addition, prospective research should validate each pathway in the particular cell type and source of interest.

Unmet Research Needs

A systematic screening of drugs applied in geriatric clinical routine on neuronal stem cell proliferation and differentiation is warranted. As a first step, this should be investigated under physiologic conditions to comprehend the basic interactions of drugs with neuronal stem cells. Subsequently, these mechanisms should be assessed in injury conditions, e.g., animal models of neurodegenerative diseases. This is of particular relevance since a number of specialized animal models exist. This includes transgenic and immunosuppressed animals in which the brain microenvironment during degeneration or after injury can be significantly different from the wild type. Moreover, drug metabolism (pharmacokinetics and dynamics) obviously differs between mice and men. Hence, it is rationale to assume that these differences may also effect any potential interactions between drugs and neuronal stem cells. However, studies investigating drug-stem cell interactions in vivo are scarce, which is why we have combined all such studies in the “injury condition” category. Hence, future research should address this question systematically in relevant disease models and shall focus on the impact of animal species and strain used.

Hence, we need to ensure that the knowledge generated from animal studies is indeed translatable to the human situation. Potential approaches involve sophisticated models mimicking a human organism, such as interconnected organs-on-a-chip. Moreover, such studies should primarily focus on combinations of stem cells with clinically applied drugs and less on purely experimental substances, and shall include comprehensive safety readout protocols.

Limitations of the Systematic Review and Meta-Analysis

Our analysis has several limitations:

i) We did not specify an *ex ante* protocol prior to the meta-analysis of the available data, including the specification of the primary outcome measure. We here performed meta-analyses on the effect of drugs used in the elderly and both the proliferation and differentiation of neuronal stem cells.

ii) We did not focus on drug effects on other stem cell functions such as migration and survival. The exclusion was made because migration is difficult to measure *in vivo* and it has different effects based on species differences.[41] On the other hand, survival, explicitly defined, is not a function of stem cells. On the contrary, integration is another function of stem cells and only shown in differentiated cells, therefore it was included in our study.

iii) The meta-analysis is currently quite limited due to the understudied effects of drugs on neuronal stem cells. However, despite the small sample size, our meta-analysis identified an interaction, which may indicate a strong effect, making these findings even more relevant. Nevertheless, more studies and particular analyses focusing on the therapeutically more frequently applied populations such as MSC are warranted.

iv) We found only publications using neuronal stem cell cultures or investigating endogenous neuronal stem cells. Further studies investigating the effect of drugs on transplanted neuronal stem cells are necessary.

v) The heterogeneity of the samples (**Table 1**) limits general conclusions.

vi) Some drugs were studied more frequently than others (**Table 2**) which can potentially over represent a single drug from a particular class or subclass leading to result bias. For example, fluoxetine dominated among the antidepressants, accounting for more than half (53.01%) of the publications in this drug class, followed by imipramine (21.69%). However, when comparing the effect of the main drug classes with their subclasses, we did not

reveal any differences (see **Table 3 and Supplemental Table 5**). In addition, the number of publications on newer antidepressant drugs was low, e.g., on sertraline (n=1) and mirtazapine (n=0). These drugs show better efficacy than fluoxetine,[42] but may have different effects on neuronal stem cell proliferation and differentiation and should therefore be investigated as well.

vii) Overall quality of the publications was relatively poor. We rarely found information on reporting of outliers (2 publications, 0.9%). Experimental evidence for the proposed underlying mechanism was provided more frequently, but still only by one third of all publications (41 records out of 115 records in the physiologic condition, 35.7%). In addition, basic statistical data such as mean and standard deviation were sometimes difficult to extract. We have tried to minimize this weakness by contacting the authors of the respective studies to obtain mean and standard deviation and where not possible measured them graphically.

The lack of clinical trials on drug-neuronal stem cell interactions, despite an increasing number of stem cell trials (only 5 trials using neuronal stem cells from a total of 120 stem cell trials in neurological disorders since January 1991, www.clinicaltrials.gov), reveals that this issue imperatively deserves more attention. Biomarkers and imaging techniques indicating neuronal stem cell proliferation and differentiation are needed to assess these processes as secondary endpoints in clinical trials.

Conclusion

The interactions between neuronal stem cells and drugs frequently used in geriatric patients are currently understudied. Despite limited data, we were able to perform a meta-analysis for the effect of antidepressants on proliferation and revealed a clear interaction. This suggests that there may be further effects of drugs that warrant further investigation under physiologic and injury conditions. This will unravel how pharmacological interventions and

391 neuronal stem cells can be combined in more efficient, safer, and ultimately successful
392 therapeutic strategies.
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394 ## Acknowledgements

395 M.I. was supported by a scholarship from the Indonesia Endowment Fund for
396 Education from Indonesia's Ministry of Finance (Award number: S-2257/LPDP.3/2016). The
397 funding source had no role in the design and conduct of the study, collection, management,
398 analysis, and interpretation of the data, preparation, review, or approval of the manuscript, and
399 decision to submit the manuscript for publication.
400 We would like to thank Andrea Maria Herrmann for her advice on the systematic
401 review and meta-analysis, as well as Dr. Larisa Bulavina for designing Figure 4.
402

403 ## Conflict of Interest

404 The authors declare that they have no conflict of interest.
405

406 ## Data Availability

407 All data that support the findings of this study are available in the manuscript and
408 supplemental data.
409

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Figure legends

Figure 1. PRISMA Flow Diagram of the Systematic Search. Of note, the number of "records" does not equal the number of publications due to experimental designs including multiple experiments, such as physiologic versus injury or physiologic versus modified conditions, representing different "records".

Figure 2. **Forest Plot of the Effect of Antidepressants under Physiologic Conditions.** We found that antidepressants stimulated neuronal stem cell proliferation (**A**, Hedges' g SMD, 0.66; 95% CI, 0.20 to 1.12; p=0.005) but not differentiation (**B**, Hedges' g SMD, 0.23; 95% CI, -0.68 to 1.13; p=0.63) under physiologic conditions. In A, the weights are given for both subgroup and overall analysis. The obtained p-values in the subgroup analysis were compared to the cutoff p-value calculated by the Holm-Bonferroni method that is a sequential method of testing p-values (from smallest to largest) to correct for multiplicity. * indicates publications from which standard deviations and means were derived by manual graphical measurement using ImageJ.

Figure 3. **Forest Plot of the Effect of Antidepressants in Models of Depression.** We identified that antidepressants increased the proliferation of stem cells in the context of stress; however the effect was not statistically significant (Hedges' g SMD, 1.14; 95% CI, -0.03 to 2.32; p=0.06). * indicates publications from which standard deviations and means were derived by manual graphical measurement using ImageJ.

Figure 4. Recorded Pathways from the Selected Publications. The mechanisms of the drugs (**A**) imipramine, fluoxetine, morphine, and (**B**) rosiglitazone, rapamycin, and insulin have been reported in a single publication each. Arrows indicate stimulation and T-shapes indicate inhibition of the subsequent substance. Positive signs indicate stimulation and negative signs indicate inhibition of the end effects (proliferation or differentiation). The straight lines indicate proven mechanism and the dotted lines indicate assumed mechanism. bcl-2: B-cell lymphoma-2; BDNF: brain-derived neurotrophic factor; BMP4: bone morphogenetic protein 4; cAMP: cyclic adenosine monophosphate; CIP1: cyclin-dependent kinase (CDK) inhibitor protein 1; CREB: cAMP response element-binding protein; FGF2: fibroblast growth factor-2; GABA: gamma-aminobutyric acid; GAD: glutamic acid decarboxylase; GDNF: glial cell-derived neurotrophic factor; GSK3ß: glycogen synthase kinase 3ß; HES-1: hairy and enhancer of split-1; IRS-1: insulin receptor substrate-1; MAPK: mitogen-activated protein kinase; NF-alpha-1: nuclear factor-alpha-1; pERK/ERK: phosphorylated extracellular signal-regulated kinases; PI3K: phosphatidylinositol-4,5-biphosphate 3-kinase; PKM: protein kinase M; SHT1Ar: serotonin-1-agonist receptor.

Table 1. **Distribution of the Records of Drug Classes and Subclasses.**

560 **Table 2. The Six Most Frequently Used Drugs Identified by the Systematic Search.**

561

562 **Table 3. Distribution of the Drug Classes Based on the Effect on Neuronal Stem Cells.**
563 The number of publications reporting a stimulating, inhibiting or neutral effect on neuronal
564 stem cell proliferation or differentiation is given. Relative percentages per drug class are
565 indicated in brackets.

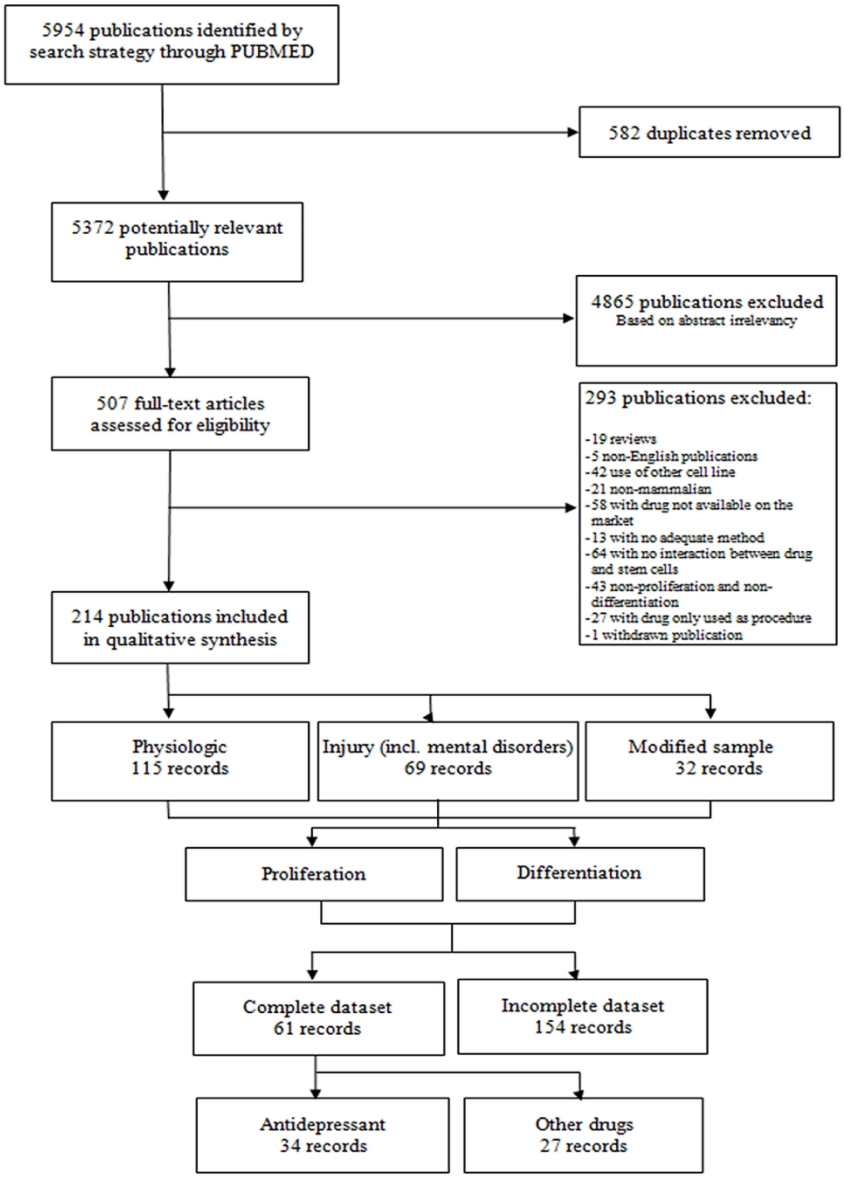

Figure 1. PRISMA Flow Diagram of the Systematic Search. Of note, the number of "records" does not equal the number of publications due to experimental designs including multiple experiments, such as physiologic versus injury or physiologic versus modified conditions, representing different "records".

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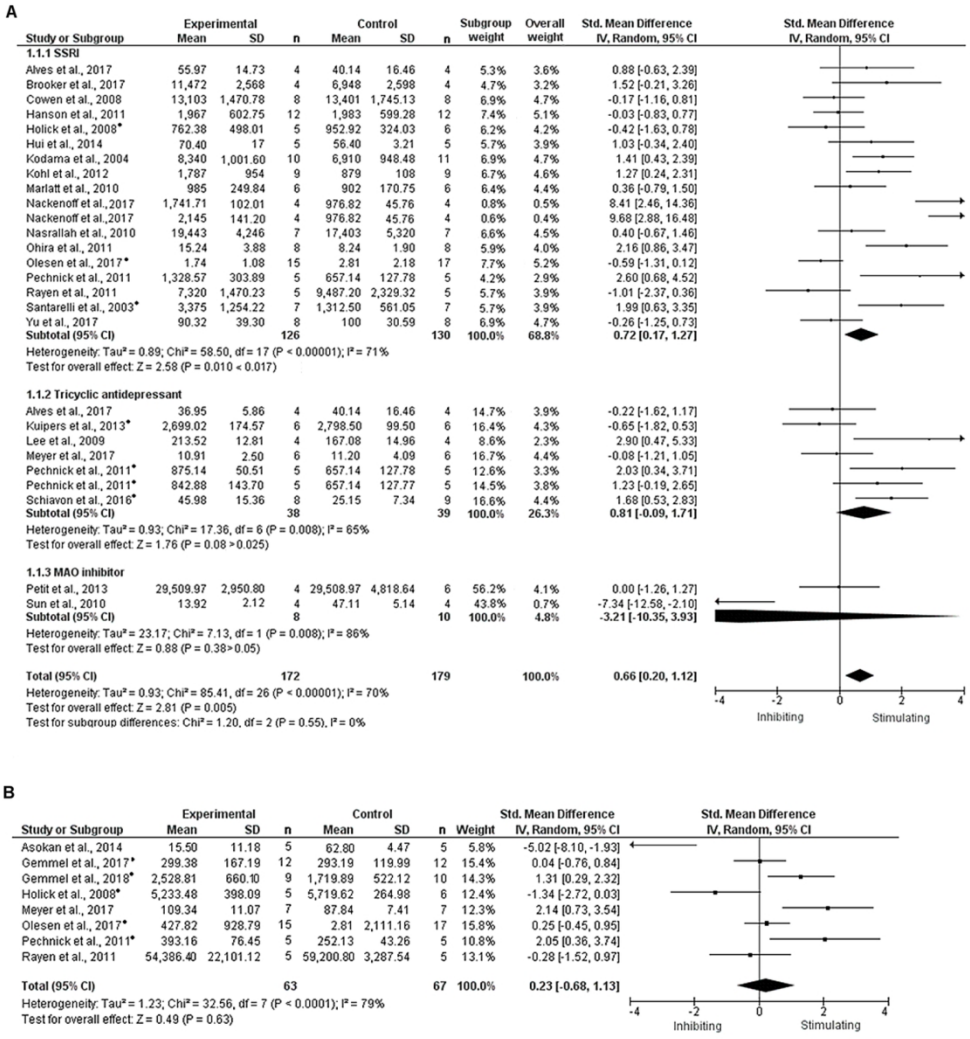

Figure 2. Forest Plot of the Effect of Antidepressants under Physiologic Conditions. We found that antidepressants stimulated neuronal stem cell proliferation (A, Hedges' g SMD, 0.66; 95% CI, 0.20 to 1.12; p=0.005) but not differentiation (B, Hedges' g SMD, 0.23; 95% CI, -0.68 to 1.13; p=0.63) under physiologic conditions. In A, the weights are given for both subgroup and overall analysis. The obtained p-values in the subgroup analysis were compared to the cutoff p-value calculated by the Holm-Bonferroni method that is a sequential method of testing p-values (from smallest to largest) to correct for multiplicity. * indicates publications from which standard deviations and means were derived by manual graphical measurement using ImageJ.

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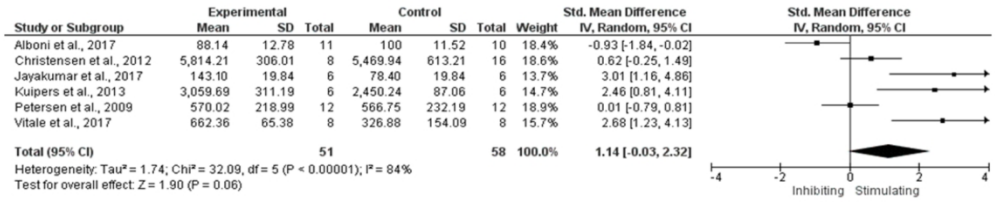

Figure 3. Forest Plot of the Effect of Antidepressants in Models of Depression. We identified that antidepressants increased the proliferation of stem cells in the context of stress; however the effect was not statistically significant (Hedges' g SMD, 1.14; 95% CI, -0.03 to 2.32; p=0.06). * indicates publications from which standard deviations and means were derived by manual graphical measurement using ImageJ.

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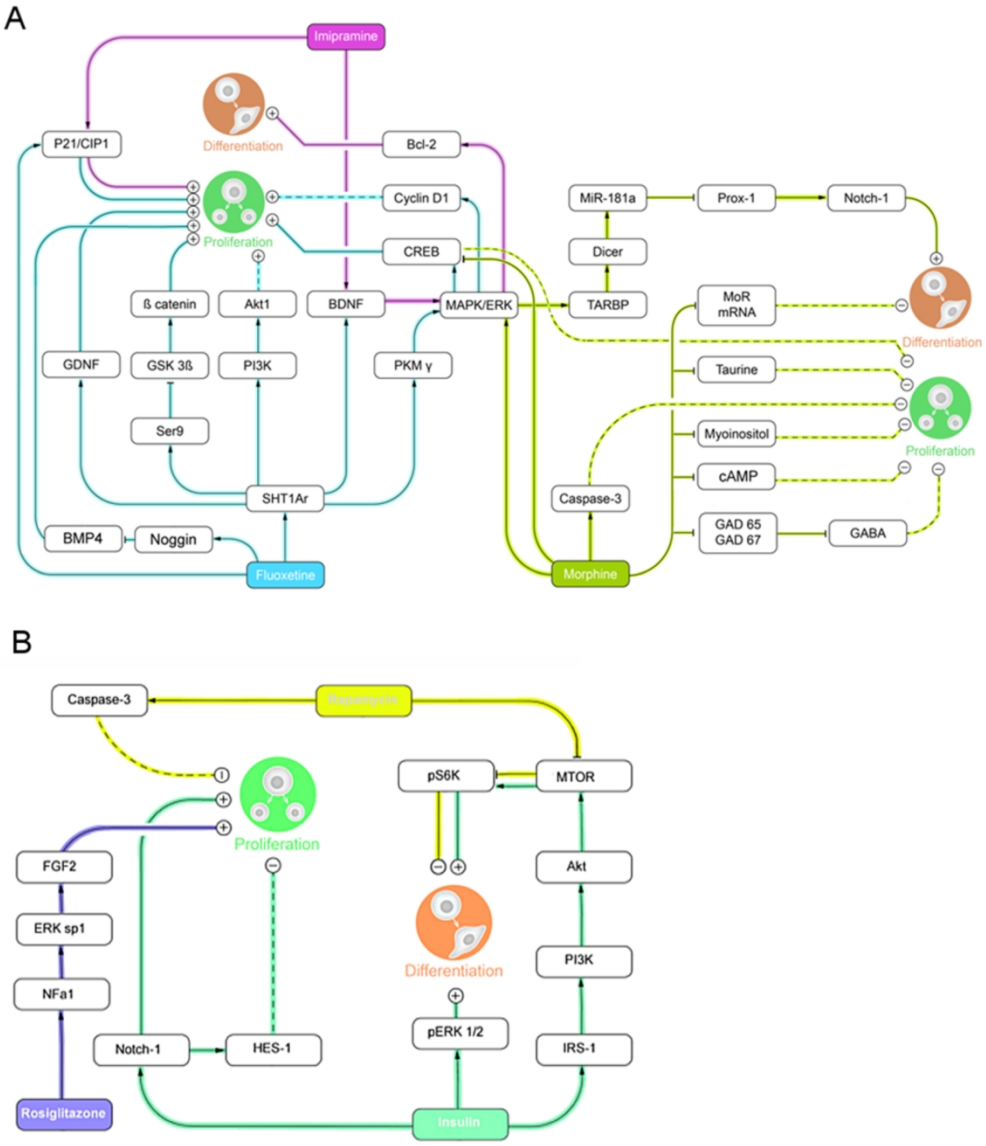

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147x170mm (300 x 300 DPI)

Table 1. **Distribution of the Records of Drug Classes and Subclasses.**

Drug class	Drug subclass	Number of records
Analgesic	Opioid	25
	Cyclooxygenase-2 inhibitor	8
	Nonsteroidal anti-inflammatory drug	7
	Total	**40**
Antibiotic	Aminoglycoside	9
	Macrolide	9
	Quinolone	6
	Tetracycline	4
	Cephalosporin	2
	Nitroimidazol	1
	Total	**31**
Antidepressant	Selective serotonin reuptake inhibitor	54
	Tricyclic antidepressant	22
	Monoamine oxidases inhibitor	5
	Atypical antidepressant	1
	Selective serotonin-norephinephrine reuptake inhibitor	1
	Total	**83**
Antidiabetic	Insulin	9
	Thiazolidinedione	9
	Incretin mimetic	3
	Non-sulfonylurea	1
	Total	**22**
Antihyperlipidemic	Statin	6
	Total	**6**

Antihypertensive	Loop diuretic	4	
	Aldosterone receptor inhibitor	3	
	Alpha 2 adrenergic agonist	3	
	Beta blocker	3	
	Calcium channel antagonist	3	
	Ace inhibitor	2	
	Angiotensin II receptor inhibitor	1	
	Total		**19**
Other drugs	Phosphodiesterase type-5	6	
	Corticosteroid	4	
	Hormonal therapy	2	
	Rho-Kinase inhibitor	2	
	Supplement	2	
	Antihelminthic	1	
	Atypical antipsychotic	1	
	Cytosine arabinoside	1	
	Triazole derivative	1	
	Total		**20**

Table 2. The Six Most Frequently Used Drugs Identified by the Systematic Search.

Drug class	Drug subclass	Drug	Number of record
Antidepressant	Selective serotonin reuptake inhibitor	Fluoxetine	44
Analgesic	Opioid	Morphine	19
Antidepressant	Atypical antidepressant	Imipramine	18
Antidiabetic	Insulin	Insulin	12
Antibiotic	Macrolide	Rapamycin	8
Antidiabetic	Thiazolidinedione	Rosiglitazone	6

Table 3. Distribution of the Drug Classes Based on the Effect on Neuronal Stem Cells. The number of publications reporting a stimulating, inhibiting or neutral effect on neuronal stem cell proliferation or differentiation is given. Relative percentages per drug class are indicated in brackets.

Drug classes	Proliferation				Differentiation		
	Stimulating	Neutral	Inhibiting		Stimulating	Neutral	Inhibiting
Analgesic	6 (19.3%)	5 (16.1%)	20 (64.5%)		6 (28.6%)	2 (9.5%)	13 (61.9%)
Antibiotic	8 (34.8%)	5 (21.7%)	10 (43.5%)		6 (24%)	7 (28%)	12 (48%)
Antidepressant	39 (65%)	15 (25%)	6 (10%)		30 (56.6%)	13 (24.5%)	10 (18.9%)
Antidiabetic	3 (37.5%)	3 (37.5%)	2 (25%)		9 (47.4%)	4 (21%)	6 (31.6%)
Antihypertensive	7 (58.3%)	3 (25%)	2 (16.7%)		7 (63.6%)	2 (18.2%)	2 (18.2%)

Supplemental Data for Manuscript

Neuronal stem cell-drug interactions: A systematic review and meta-analysis

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Search Strategies

Search terms:

1. Neurogenesis [All Fields]
2. Neuronal cell therapy [All Fields]
3. Neuronal precursor cell [All Fields] OR Neuronal progenitor cell [All Fields]
4. Neuronal cell proliferation [All Fields]
5. Neuronal cell differentiation [All Fields]
6. #1 OR #2 OR #3 OR #4 OR #5
7. Statin [All Fields]
8. PCSK9 Inhibitor [All Fields]
9. Bile acid sequestrant [All Fields]
10. Alpha 2 adrenergic receptor agonist [All Fields]
11. Beta adrenergic receptor antagonist [All Fields]
12. Beta blocker [All Fields]
13. Angiotensin II Receptor Inhibitor [All Fields] OR ARB [All Fields]
14. Alpha glucosidase inhibitor [All Fields]
15. Amylin analogs [All Fields]
16. Dipeptyl peptidase 4 inhibitor [All Fields]
17. SGLT 2 Inhibitor [All Fields]
18. Incretin mimetics [All Fields]
19. Insulin [All Fields]
20. Meglitinides [All Fields]
21. Sulfonylurea [All Fields]
22. Non sulfonylurea [All Fields]
23. Loop diuretics [All Fields]
24. Calcium channel antagonist [All Fields]
25. Thiazolidinediones [All Fields]
26. Norephinephrine and dopamine receptor Inhibitor [All Fields] OR NDRI [All Fields]
27. Selective serotonin reuptake inhibitor [All Fields] OR SSRI[All Fields]
28. Serotonin and Norephinephrine Reuptake Inhibitor [All Fields] OR SNRI[All Fields]
29. Atypical Antidepressant [All Fields]
30. Potassium diuretics [All Fields]
31. Aldosterone receptor antagonist [All Fields]
32. Tricyclic antidepressant [All Fields]
33. Monoamine oxidase Inhibitor [All Fields] OR MAOI [All Fields]
34. Acetaminophen [All Fields] OR paracetamol [All Fields]
35. Nonsteroidal anti-inflammatory drug [All Fields] OR NSAID [All Fields]
36. Thiazide diuretics [All Fields]
37. Carbapenem [All Fields]
38. Penicillin [All Fields]
39. Tetracyclin [All Fields]
40. Cephalosporin [All Fields]
41. Quinolone [All Fields]
42. Lincomycin [All Fields]
43. Macrolide [All Fields]
44. Sulfonamide [All Fields]
45. Glycopeptide [All Fields]
46. Aminoglycoside [All Fields]
47. Opioid [All Fields]
48. COX-2 Inhibitor [All Fields]
49. #7 OR #8 OR #9 OR #10 OR#11 OR #12 OR#13 OR#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR#29 OR #30

OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48

50. #6 AND #49

Supplemental Table 1. Excluded Publications, With the Reasons for Their Exclusion.

No	Author, Year	PMID	Review	Non-English publication	Use other cell line	Non-mammalian animal	Non-available drug in the market	No adequate method	No interaction between drug and the stem cell	Non-Proliferation or Non Differentiation marker	Drug only used as procedure	Withdrawn article
1.	Abdelkader et al., 2017	28178754							*			
2.	Abdipranoto-Cowley et al., 2009	19489097					*					
3.	Aldkogius et al., 2009	19544468									*	
4.	Allani et al., 2018	29788733								*		
5.	Altinay et al., 2017	27593816					*					
6.	Aoki et al., 1993	16350568							*			
7.	Ashjian et al., 2003	14556988									*	
8.	Ayuob, 2017	27444866					*					
9.	Bae et al., 2017	29165354	*									
10.	Baka et al., 2004	15290185			*							
11.	Banks, 2012	22612379						*				
12.	Baravalle et al., 2017	27616271							*			
13.	Bassani et al., 2017	28801114					*					
14.	Bassani et al., 2018	28623617									*	
15.	Bateman & McNeill, 2006	16786222	*									
16.	Beech et al., 2004	15176089									*	
17.	Belovicova et al., 2017	28456144								*		
18.	Bernstein et al., 2014	24817634							*			
19.	Bianchi et al., 2017	29149058	*									
20.	Biggio et al., 2009	19309534					*					
21.	Boldrini et al., 2012	22652019								*		
22.	Borg et al., 2014	24898143							*			
23.	Bottcher et al., 2000	10837202			*							
24.	Bottcher et al., 2004	15584921						*				
25.	Boucher et al., 1998	9579401				*						

No	Author, Year	PMID	Review	Non-English publication	Use other cell line	Non-mammalian animal	Non-available drug in the market	No adequate method	No interaction between drug and the stem cell	Non-Proliferation or Non Differentiation marker	Drug only used as procedure	Withdrawn article
26.	Brenza et al., 2017	27771430					*					
27.	Brooker et al., 2000	10679768					*					
28.	Brownjohn et al., 2017	28285880							*			
29.	Brustein et al., 2012	22888055				*						
30.	Burgdorf et al., 2017	28158790							*			
31.	Buzanska et al., 2009	19609937								*		
32.	Cabras et al., 2010	20356437								*		
33.	Calabria et al., 2008	18039545			*							
34.	Calderari et al., 2017	28911974					*					
35.	Campos et al., 2017	28588483	*									
36.	Cao et al., 2018	29736175	*									
37.	Carlson et al., 2018	29455576					*					
38.	Carson et al., 2012	3225598			*							
39.	Castilho et al., 2000	10877919								*		
40.	Cebolla et al., 2008	18579744							*			
41.	Cerri et al., 2015	26198165								*		
42.	Chalicem et al., 2017	28747063	*									
43.	Chao et al., 2013	23691054								*		
44.	Chen et al., 2005	15895831			*							
45.	Chen et al., 2012	23317920								*		
46.	Chesnokova & Pechnick, 2008	18682686	*									
47.	Chiba et al., 2010	19925560								*		
48.	Chilmonczyk et al., 2017	28324844	*									
49.	Choi et al., 2017	28045430					*					
50.	Cocchiarella, 2012	22256833						*				
51.	Cominski et al., 2012	22280973							*			

No	Author, Year	PMID	Review	Non-English publication	Use other cell line	Non-mammalian animal	Non-available drug in the market	No adequate method	No interaction between drug and the stem cell	Non-Proliferation or Non Differentiation marker	Drug only used as procedure	Withdrawn article
52.	Cominski et al., 2014	25086317							*			
53.	Compagnucci et al., 2015	27160703								*		
54.	Conner et al., 2012	22595793					*					
55.	Coplan et al., 2014	25506432							*			
56.	Corso et al., 1998	9514310			*							
57.	Culberson et al., 2017	28253982	*									
58.	Czeh et al., 2001	11675510								*		
59.	De la Rosa et al., 1994	7535629				*						
60.	De Pablo et al., 1996	9087719	*									
61.	Diaz et al., 1999	10215915				*						
62.	Diaz et al., 2000	10725240				*						
63.	Dikmen, 2017	28338387					*					
64.	Dobarro et al., 2013	22824191						*				
65.	Doze et al., 2011	21791575			*							
66.	Einoch et al., 2017	28410959								*		
67.	Eisch & Mandyam, 2004	14992964	*									
68.	Ekström et al., 1993	8215035				*						
69.	Ericksson et al., 1992	1382177					*					
70.	Ericksson et al., 2008	18293414								*		
71.	Faijerson et al., 2009	19425175					*					
72.	Faivre et al., 2011	21273318							*			
73.	Faivre et al., 2012	22115896					*					
74.	Farrar et al., 2005	16304629					*					
75.	Ferrucci et al., 2017	28418837			*							
76.	Fesharaki et al., 2018	29633593			*							
77.	Fischer et al., 2002a	12435364				*						
78.	Fischer et al., 2002b	12417664				*						

No	Author, Year	PMID	Review	Non-English publication	Use other cell line	Non-mammalian animal	Non-available drug in the market	No adequate method	No interaction between drug and the stem cell	Non-Proliferation or Non Differentiation marker	Drug only used as procedure	Withdrawn article
79.	Fischer et al., 2002c	12176172				*						
80.	Fischer et al., 2003	12871698				*						
81.	Fishwick et al., 2010	20004186				*						
82.	Foerster et al., 2017	27993979			*							
83.	Furuya et al., 2009	19651108								*		
84.	Garcia-de lacoba et al.,1999	9886830				*						
85.	Garcia-Perez et al., 2017	26742526			*							
86.	Geng et al., 2017	28782906			*							
87.	Goto et al., 2011	22025691						*				
88.	Goudarzi et al., 2018	29870058			*							
89.	Gu et al., 2017	28916193			*							
90.	Guo et al., 2010	20466036							*			
91.	Guo et al., 2017	28382978								*		
92.	Guo et al., 2017	28865290								*		
93.	Hafizi et al., 2012	23054438							*			
94.	Hahn et al., 2010	19895666							*			
95.	Hansel et al., 2001	11598996					*					
96.	Hao et al., 2017	27743319			*							
97.	Harburg et al., 2007	17055658							*			
98.	Hartman et al., 2013	24139800							*			
99.	Hauser et al., 1993	8244536								*		
100.	Hayashi et al., 2012	22293695		*								
101.	Hays et al., 2012	22061798			*							
102.	Hay-Schmidt et al., 2017	28559473							*			
103.	Heanue et al., 2011	21280162									*	
104.	Heidenreich et al., 1996	8626622				*						
105.	Hernandez-Sanchez et al., 1995	7568228				*						

No	Author, Year	PMID	Review	Non-English publication	Use other cell line	Non-mammalian animal	Non-available drug in the market	No adequate method	No interaction between drug and the stem cell	Non-Proliferation or Non Differentiation marker	Drug only used as procedure	Withdrawn article
106.	Hicks et al., 2000	11090640					*					
107.	Hidaka et al., 2013	23673084									*	
108.	Hiramoto et al., 2008	18446092								*		
109.	Hitchcock et al., 2001	11481281				*						
110.	Hori et al., 2005	15839736							*			
111.	Hoshimaru et al., 1996	8643664									*	
112.	Huang et al., 2017	28026149			*							
113.	Huong et al., 2011	22130242						*				
114.	Inta et al., 2016.	27352782	*									
115.	Isaev et al., 2018	29684395								*		
116.	Ishizuka et al., 2014	25058791					*					
117.	Ito & Araki, 2010	20048438		*								
118.	Jimenez-Gonzalez et al., 2017	29111275			*							
119.	Jin et al., 2017	27324897								*		
120.	Jukic et al., 2017	27895323							*			
121.	Katz et al., 2016	26772642			*							
122.	Kazma et al., 2010	19746435							*			
123.	Khurshid et al., 2010	20495180				*						
124.	King et al., 2017	28076682								*		
125.	Kisoh et al., 2017	27866373					*					
126.	Kitani et al., 1991	1917779									*	
127.	Klawitter et al., 2015	25912929	*									
128.	Koch et al., 2012	22510327							*			
129.	Kolarova et al., 2003	13129439					*					
130.	Kolodziej et al., 2008	18331339							*			
131.	Kompisch et al., 2010	20945072									*	
132.	Kozlova & Jansson, 2009	19421078							*			

No	Author, Year	PMID	Review	Non-English publication	Use other cell line	Non-mammalian animal	Non-available drug in the market	No adequate method	No interaction between drug and the stem cell	Non-Proliferation or Non Differentiation marker	Drug only used as procedure	Withdrawn article
133.	Kuhmonen et al., 1997	9286902						*				
134.	Kwon et al., 1998	23392671								*		
135.	Lafourcade et al., 2013	23392671			*							
136.	Lai et al., 2011	21933448			*							
137.	Landry et al., 2011	21762764			*							
138.	Lang et al., 2009	19596361							*			
139.	Lecomte et al., 2017	28396216			*							
140.	Lee et al., 2007	17707770								*		
141.	Lehmann et al., 2013	23407954			*							
142.	Lennox et al., 2013	23138973					*					
143.	Leslie et al., 1998	9729266							*			
144.	Li et al., 2000	10956432									*	
145.	Li et al., 2012	22752192									*	
146.	Li et al., 2017	27590141					*					
147.	Liu et al., 2007	17663584					*					
148.	Liu et al., 2017	28339691					*					
149.	Lixing et al., 2017	29129800					*					
150.	Lu et al., 1996	8816274							*			
151.	Lucassen et al., 2004	15050859								*		
152.	Ma et al., 2017	28430602								*		
153.	Ma EY et al., 2008	18305259			*							
154.	Malaterre et al., 2003	12918022				*						
155.	Manev et al., 2001	11462800					*					
156.	Mao et al., 2005	16221970							*			
157.	Martone et al., 2014	24689961			*							
158.	Marxreiter et al., 2009	19291219									*	
159.	Masuda et al., 2012	21914456								*		

No	Author, Year	PMID	Review	Non-English publication	Use other cell line	Non-mammalian animal	Non-available drug in the market	No adequate method	No interaction between drug and the stem cell	Non-Proliferation or Non Differentiation marker	Drug only used as procedure	Withdrawn article
160.	Matrisciano et al., 2008	18082849					*					
161.	Mazur-Kolecka et al., 2006	17112488					*					
162.	Mazur-Kolecka et al., 2012	16105709					*					
163.	McCreedy et al., 2014	25346848									*	
164.	McEwen & Chattarji, 2004	15550348	*									
165.	McGovern et al., 2012	22867941					*					
166.	McNeill et al., 2008	18505882							*			
167.	Mehta et al., 2017	28939429					*					
168.	Mendez-David et al., 2015	25916883					*					
169.	Menendez & Vazquez-Martin, 2012	22935702	*									
170.	Mertens et al., 2013	24371804								*		
171.	Min et al., 2011	21471976			*							
172.	Min et al., 2017	28601633					*					
173.	Mir et al., 2017	28607354					*					
174.	Miyamoto et al., 2011	21626864		*								
175.	Mogi et al., 2012	22868412								*		
176.	Moon et al., 2013	23224631							*			
177.	Morel et al., 2017	28405590					*					
178.	Mostany et al., 2008	18511088							*			
179.	Motaghinejad et al., 2017	28082019								*		
180.	Mrkusich et al., 2004	14766199							*			
181.	Na et al., 2017	28966575			*							
182.	Naoi et al., 2018	28293733	*									
183.	Narita et al., 2006	16696856					*					
184.	Nataf & Monier, 1992	1358479									*	
185.	Nava et al., 2017	26523035								*		
186.	Newton & Duman, 2007	17696572	*									

No	Author, Year	PMID	Review	Non-English publication	Use other cell line	Non-mammalian animal	Non-available drug in the market	No adequate method	No interaction between drug and the stem cell	Non-Proliferation or Non Differentiation marker	Drug only used as procedure	Withdrawn article
187.	Nieto et al., 2017	28794445					*					
188.	Niu et al., 2017	28179206					*					
189.	Noor et al., 2017	29147492							*			
190.	Norambuena et al., 2017	27693185							*			
191.	Novozhilova et al., 2015	25514049					*					
192.	Ohmasa & Saito, 2004	15140564									*	
193.	Olianas et al., 2017	28815598							*			
194.	Olivius et al., 2003	12850564									*	
195.	Omar et al., 2017	28801265							*			
196.	Ostapcuk et al., 2018	29795351							*			
197.	Otsuki et al., 2018	29622651							*			
198.	Palazuelos et al., 2012	22102284					*					
199.	Pan et al., 2016	26873855							*			
200.	Park et al., 2017	29299155			*							
201.	Park et al., 2002	12213294									*	
202.	Parmar et al., 2017	28164768			*							
203.	Parng et al., 2007	16769228							*			
204.	Parween et al., 2017	29311838							*			
205.	Patnaik et al., 2016	7807796								*		
206.	Pfisterer et al., 2016	27917895								*		
207.	Pixley et al., 1998	9929614						*				
208.	Popova et al., 2018	28887184						*				
209.	Powell et al., 2017	28394502			*							
210.	Pradillo et al., 2017	27856349					*					
211.	Procaccini et al., 2011	21073553					*					
212.	Qiu et al., 2018	29165691							*			

No	Author, Year	PMID	Review	Non-English publication	Use other cell line	Non-mammalian animal	Non-available drug in the market	No adequate method	No interaction between drug and the stem cell	Non-Proliferation or Non Differentiation marker	Drug only used as procedure	Withdrawn article
213.	Quartier et al 2018	29428674						*				
214.	Quinta et al., 2010	20796173						*				
215.	Quinte et al., 2012	22091865								*		
216.	Rachmani et al., 2013	24024202								*		
217.	Ramalingayya et al., 2017	28408800			*							
218.	Ramkumar et al., 2017	28420370			*							
219.	Ramos-Rodriguez et al., 2014	24586614							*			
220.	Ray et al., 1999	10473288							*			
221.	Raymon et al., 1999	10377351									*	
222.	Revsin et al., 2005	15748869						*				
223.	Ridet et al., 1999	10022551									*	
224.	Riederer et al., 2017	27998194	*									
225.	Robinson et al., 1994	7988444				*						
226.	Rossi et al., 2018	29531474				*						
227.	Safford et al., 2002	12051722									*	
228.	Sagir et al., 2017	28461249			*							
229.	Sairanen et al., 2007	17049169			*							
230.	Sajan et al., 2017	29032894					*					
231.	Saliba et al., 2017	28143498								*		
232.	Salzberg et al., 2017	28114319							*			
233.	Sanchez Simon et al., 2012	22062135				*						
234.	Santa-Olalla et al., 1995	8568917					*					
235.	Santos et al., 2017	27871898			*							
236.	Sargeant et al., 2007	17888889							*			
237.	Sarkar & Das, 2003	14511111			*							
238.	Sarlak et al., 2013	23985544					*					
239.	Scheller et al., 2017	28274821					*					

No	Author, Year	PMID	Review	Non-English publication	Use other cell line	Non-mammalian animal	Non-available drug in the market	No adequate method	No interaction between drug and the stem cell	Non-Proliferation or Non Differentiation marker	Drug only used as procedure	Withdrawn article
240.	Schmidt et al., 1999	10631639						*				
241.	Schmidt et al., 2015	25470346					*					
242.	Schmitz et al., 2018	29324300							*			
243.	Selden et al., 2013	23581634									*	
244.	Sevc et al., 2013	23748136								*		
245.	Sheng et al., 2007	17538007							*			
246.	Shin et al., 2004	14999075							*			
247.	Singer et al., 2009	19363795							*			
248.	Singh et al., 1997	9163577								*		
249.	Smith-Arica et al., 2000	11124058							*			
250.	Solbrig et al., 2006	16399805									*	
251.	Stranahan et al., 2008	18278039									*	
252.	Suh et al., 2005	15677508							*			
253.	Tai et al., 2018	29050859					*					
254.	Tan et al., 2018	29635048							*			
255.	Tian et al., 2017	28663724					*					
256.	Tondreau et al., 2008	18405367							*			
257.	Tong et al., 1997	9192297								*		
258.	Tramutola et al., 2017	27715341	*									
259.	Tripathi et al., 2008	18455254							*			
260.	Trivedi et al., 2016	27611101								*		
261.	Tzeng et al., 2018	29463001					*					
262.	Umschweif et al., 2014	24957202					*					
263.	Uyanigkgil et al., 2004	14963685							*			
264.	Val-Laillet et al., 2017	29242276					*					
265.	Van Gorp et al., 2013	23710605									*	
266.	Varghese, eta l., 2017	29147115			*							

No	Author, Year	PMID	Review	Non-English publication	Use other cell line	Non-mammalian animal	Non-available drug in the market	No adequate method	No interaction between drug and the stem cell	Non-Proliferation or Non Differentiation marker	Drug only used as procedure	Withdrawn article
267.	Vicario-Abejon et al., 2003	12574418					*					
268.	Vilchez et al., 2013	23551888							*			
269.	Waetzig, et al., 2017	28479141			*							
270.	Wang et al., 2016	25567530					*					
271.	Wang et al., 2003	12801891							*			
272.	Wang et al., 2017	28780644					*					
273.	Wang G et al., 2017	28780644							*			
274.	Wong chitrat et al., 2016	27620814							*			
275.	Wu et al., 2013	23357262		*								
276.	Xiong et al., 2009	18726712								*		
277.	Yamashita et al., 1995	7724532			*							
278.	Yanagisawa et al., 2009	19598243								*		
279.	Yanai et al., 2016	27229654							*			
280.	Yang et al., 2006	16955841		*								
281.	Yilmaz et al., 2014	24831366			*							
282.	Ying et al., 2002	11932748							*			
283.	Ying et al., 2012	22569742									*	
284.	Yoles et al., 1999	9888428			*							
285.	Yoon et al., 2013	24095011					*					
286.	Yu et al., 2005	15789426									*	
287.	Zackenfels et al., 1995	7718236				*						
288.	Zang et al., 2017	28456716							*			
289.	Zhang et al., 2004	15026250									*	
290.	Zhang et al., 2008	17854417							*			
291.	Zhang et al., 2017	28842345					*					
292.	Zhao et al., 2007	17980966								*		
293.	Zheng & Chen, 2007	17687392										*

Supplemental Table 2. Distribution of the Records in the Injury and Modified Subgroup. *PDE5: Phosphodiesterase type-5; SSRI: Selective serotonin reuptake inhibitor; NSAID: Nonsteroidal anti-inflammatory drug; COX 2: Cyclooxygenase-2; ROCK: Rho-associated protein kinase.*

Condition	Type of experiment		Number of records
Injury including mental disorders	Ischemia/hypoxia		20
		Sildenafil (PDE5) 5	
		Fluoxetine (SSRI) 3	
		Aripriprazole (Quinolone) 2	
		Atorvastatin (Statin) 2	
		Bumetanide (Loop diuretic) 2	
		Indomethacin (NSAID) 2	
		Celecoxib (COX2 inhibitor) 1	
		Citalopram (SSRI) 1	
		Fasudil (ROCK inhibitor) 1	
		Glibenclamid (Non-sulfonylurea) 1	
	Depression		17
		Fluoxetine (SSRI) 8	
		Amitriptiline (Tricyclic antidepressant) 1	
		Aripriprazole (Quinolone) 1	
		Clozapine (Atypical antipsychotic) 1	
		Gaboxadol (SSRI) 1	
		Imipramine (Tricyclic antidepressant) 1	
		Morphine (Opioid) 1	
		Nortriptyline (Tricyclic antidepressant) 1	
		Tianeptine (Tricyclic antidepressant) 1	
		Combination of different SSRIs 1	
	Febril seizures/epilepsy		5
	Metabolic disorder		5
	Parkinson's disease		4

	Alzheimer's disease	3
	Traumatic brain injury	3
	Lipopolysaccharide treatment	3
	Inflammation	2
	Spinal cord injury	2
	Alcoholic animal	1
	Avoidance test (electricity)	1
	Bulbectomy	1
	Huntington's disease	1
	Intracerebral hemorrhagic	1
	Whole brain irradiation	1
Modified	Transgenic	12
	Drug combination	7
	Conditioned environment/modification	5
	Corticosteroid treatment	4
	Conditioned diet	2
	Heroin extinction	1

Supplemental Table 3. Distribution of the Records According to the Sample Source.

No	Condition	Author, Year	Type of experiment				Source of cells				Location of the cells		
			In vitro	In vivo	In utero	Ex vivo	Rat	Mouse	Human	Other mammals (e.g., Guinea pigs or Mongolian Gerbils)	Hippocampus /Subgranular zone/Dentate gyrus	Subventricular / periventricular zone	Other regions (e.g., Striato-pallidum complex, mesenchepalon, spinal cord, hypothalamus)
1	Physiologic	Alvarez et al., 2009,		*				*					
2		Alves et al.,2017		*			*				*		
3		Amellem et al., 2017		*				*			*		
4		Arguello et al., 2008		*				*			*		
5		Arguello et al., 2009		*				*			*		
6		Arsenijevic et al., 1998	*					*					*
7		Asokan et al., 2014		*			*				*		
8		Bath et al., 2017		*			*				*		
9		Beauquis et al., 2006		*				*			*		
10		Brooker et al., 2017		*				*			*		
11		Chang et al., 2008,		*				*			*		
12		Chen et al., 2013		*				*			*		
13		Chen et al., 2018		*						*	*		
14		Chen et al., 2018		*				*			*		
15		Christie et al., 2012,		*			*				*		
16		Cowen et al., 2008		*			*				*		
17		Deng et al., 2015	*				*					*	
18		Desai et al., 2011		*			*						*
19		Desai et al., 2011	*				*						*
20		Dholakiya et al., 2016	*					*					*
21		Eisch et al., 2000	*				*				*		
22		Fex Svenningsen et al., 1996	*				*						*
23		Fischer et al., 2008		*				*			*		

No	Condition	Author, Year	Type of experiment				Source of cells				Location of the cells		
			In vitro	In vivo	In utero	Ex vivo	Rat	Mouse	Human	Other mammals (e.g., Guinea pigs or Mongolian Gerbils)	Hippocampus /Subgranular zone/Dentate gyrus	Subventricular / periventricular zone	Other regions (e.g., Striato-pallidum complex, mesenchepalon, spinal cord, hypothalamus)
24		Gatt et al., 2017	*						*		*		
25		Gemmel et al., 2017		*			*				*		
26		Gemmel et al., 2018		*			*				*		
27		Ghoochani et al., 2011	*					*					*
28		Gomez-pinedo et al., 2010		*			*				*		
29		Gupta et al., 2009	*					*				*	
30		Han et al., 2008	*				*						*
31		Han et al., 2011		*				*			*		
32		Hanson et al., 2011		*			*				*		
33		Hauser et al., 2000	*					*					*
34		Holick et al., 2008		*				*			*		
35		Huang et al., 2007	*				*				*		
36		Hui et al., 2014	*				*				*		
37		Hunter et al., 2012		*				*			*		
38		Jackson-guilford et al., 2000		*			*				*		
39		Jenrow et al., 2010		*			*				*		
40		Jhaveri et al., 2010	*					*			*		
41		Kahn et al., 2005		*			*				*		
42		Kanakasabai et al., 2012	*					*					*
43		Kang et al., 2017	*						*				*
44		Kawahara et al., 2012				*				*			*
45		Keilhoff et al., 2006		*			*				*	*	
46		Kelland et al., 2014	*						*				*

No	Condition	Author, Year	Type of experiment				Source of cells				Location of the cells		
			In vitro	In vivo	In utero	Ex vivo	Rat	Mouse	Human	Other mammals (e.g., Guinea pigs or Mongolian Gerbils)	Hippocampus /Subgranular zone/Dentate gyrus	Subventricular / periventricular zone	Other regions (e.g., Striato-pallidum complex, mesenchepalon, spinal cord, hypothalamus)
47		Kim et al., 2006	*				*						*
48		Kitamura et al., 2015		*			*				*		
49		Kitamura et al., 2017		*			*				*		
50		Kodama et al., 2004		*			*				*		*
51		Kohl et al., 2012		*				*			*		
52		Kota et al., 2015	*				*		*		*		
53		Kudo et al., 2003	*					*					*
54		Kumihashi et al., 2001		*						*	*		
55		Kusakawa et al., 2010	*					*					*
56		Lee et al., 2009		*				*			*		
57		Lee et al., 2010		*				*			*		
58		Lee et al., 2016	*						*				*
59		Li et al., 2014	*				*						*
60		Li et al., 2017	*						*				*
61		Liu et al., 2017		*			*				*		
62		Marlatt et al., 2010		*				*			*		
63		Meneghini et al., 2014		*				*			*		
64		Meyer et al., 2017		*				*			*	*	
65		Mishra et al., 2017		*			*				*		
66		Misumi et al., 2008	*				*						*
67		Monje et al., 2003		*			*				*		
68		Nackenoff et al., 2017		*				*			*		
69		Nam et al., 2015		*				*			*		
70		Nasrallah et al., 2010		*			*				*		

No	Condition	Author, Year	Type of experiment				Source of cells				Location of the cells		
			In vitro	In vivo	In utero	Ex vivo	Rat	Mouse	Human	Other mammals (e.g., Guinea pigs or Mongolian Gerbils)	Hippocampus /Subgranular zone/Dentate gyrus	Subventricular / periventricular zone	Other regions (e.g., Striato-pallidum complex, mesenchepalon, spinal cord, hypothalamus)
71		Ohira et al., 2011		*				*			*		
72		Olesen et al., 2017		*				*			*		
73		Opanashuk et al., 1998	*					*					*
74		Paliouras et al., 2012	*					*				*	*
75		Park et al., 2013		*				*			*		
76		Patnaik et al., 2016	*						*				*
77		Pechnick et al., 2008		*				*			*		
78		Pechnick et al., 2011		*				*			*		
79		Peng et al., 2008		*			*				*		
80		Pereira et al.,2013	*					*					*
81		Persson et al., 2003	*				*				*		
82		Petit et al., 2013		*				*					*
83		Pettit et al., 2012		*				*			*		
84		Piacentini et al., 2008	*					*					*
85		Ping et al., 2013		*				*			*		
86		Rayen et al., 2011			*		*				*		
87		Sah et al., 1997	*						*				*
88		Sankararaman et al., 2012		*			*				*		
89		Santarelli et al., 2003		*				*			*		
90		Schiavon et al., 2016		*				*				*	
91		Skardelly et al., 2013	*						*				*
92		Sugimoto et al., 2008	*					*					*
93		Sultan et al., 2013		*				*			*		

No	Condition	Author, Year	Type of experiment				Source of cells				Location of the cells		
			In vitro	In vivo	In utero	Ex vivo	Rat	Mouse	Human	Other mammals (e.g., Guinea pigs or Mongolian Gerbils)	Hippocampus /Subgranular zone/Dentate gyrus	Subventricular / periventricular zone	Other regions (e.g., Striato-pallidum complex, mesenchepalon, spinal cord, hypothalamus)
94		Sun et al., 2010	*					*					*
95		Sun et al., 2013	*					*					*
96		Sun et al., 2015		*			*				*		
97		Sun et al., 2018		*			*				*		
98		Teh et al., 2014	*				*				*		
99		Toran-allerand et al., 1991	*					*					*
100		Traudt et al., 2012		*			*				*		
101		Tsai et al., 2010	*				*						*
102		Uchida et al., 2002		*			*				*		
103		Wang et al., 2011		*				*			*		
104		Wang et al., 2014	*				*				*		
105		Wang et al., 2017		*				*					*
106		Willner et al., 2014	*					*					*
107		Wu et al., 2014			*		*						*
108		Xu et al., 2006		*			*				*		
109		Xu et al., 2014		*				*			*		
110		Xu et al., 2015		*				*			*		
111		Xu et al., 2017		*			*					*	
112		Yoneyama et al., 2014		*				*			*		
113		Yu et al., 2017		*			*				*		
114		Zheng et al., 2013		*				*			*		
115		Zusso et al., 2008	*				*						*
116	Injury (incl.	Alboni et al., 2017		*				*			*		

No	Condition	Author, Year	Type of experiment				Source of cells				Location of the cells		
			In vitro	In vivo	In utero	Ex vivo	Rat	Mouse	Human	Other mammals (e.g., Guinea pigs or Mongolian Gerbils)	Hippocampus /Subgranular zone/Dentate gyrus	Subventricular / periventricular zone	Other regions (e.g., Striato-pallidum complex, mesenchepalon, spinal cord, hypothalamus)
117	mental disorders)	Bastos et al., 2008		*				*			*		
118		Biscaro et al., 2012		*				*			*		
119		Boldrini et al., 2009	*						*		*		
120		Chadwick et al., 2011		*				*			*		
121		Chang et al., 2006		*			*				*		
122		Chen et al., 2003		*			*				*		
123		Chen et al., 2008		*			*					*	
124		Chiu et al., 2014		*				*					*
125		Christensen et al., 2012		*			*				*		
126		Ding et al., 2010		*				*			*		
127		Duan et al., 2008		*				*			*	*	
128		Engels et al., 2016		*				*					*
129		Espinera et al., 2013		*				*			*		
130		Gault e tal., 2015		*				*			*		
131		Gobinath et al., 2017		*			*				*		
132		Gobinath et al., 2018		*			*				*		
133		Goldshmit et al., 2015		*				*					*
134		Goncalves et al., 2010		*				*				*	
135		Guan et al., 2015	*				*				*		
136		Hays et al., 2013		*			*				*		
137		He et al., 2008		*				*				*	
138		Hoehn et al., 2005,		*			*						*
139		Hsieh et al., 2017		*			*				*		
140		Hu, et al., 2017		*			*				*		
141		Hwang et al., 2010		*			*				*		
142		Jaako et al., 2009		*				*			*		
143		Jaako-movits et al., 2006		*			*						*

No	Condition	Author, Year	Type of experiment				Source of cells				Location of the cells		
			In vitro	In vivo	In utero	Ex vivo	Rat	Mouse	Human	Other mammals (e.g., Guinea pigs or Mongolian Gerbils)	Hippocampus /Subgranular zone/Dentate gyrus	Subventricular / periventricular zone	Other regions (e.g., Striato-pallidum complex, mesenchepalon, spinal cord, hypothalamus)
144		Jayakumar et al., 2017		*			*				*		
145		Jenrow et al., 2011		*			*				*		
146		Jung et al., 2006	*	*			*		*		*		*
147		Khodanovich et al., 2017		*			*				*		
148		Kim et al., 2015		*				*			*		
149		Kim et al., 2017	*					*					*
150		Kuipers et al., 2013		*			*				*		
151		Li et al., 2009		*				*			*		
152		Lu et al., 2007		*			*				*		
153		Lu et al., 2014		*				*			*		
154		Ma et al., 2015		*			*				*		
155		Malberg et al., 2003		*			*				*		
156		Marissal-Arvy et al., 2018		*			*				*		
157		Matsuda et al., 2017		*				*			*		
158		McClean et al., 2013		*				*			*		
159		Meng et al., 2011		*			*						*
160		Morais et al., 2014		*			*				*		
161		Morais et al., 2017		*			*				*		
162		Ortega et al., 2013		*			*						*
163		Ou-Yang et al., 2016		*			*				*		
164		Petersen et al., 2009		*			*				*		
165		Ramos-Rodriguez et al., 2017		*				*				*	
166		Sasaki et al., 2003		*				*			*		
167		Seyfried et al., 2008		*					*				*
168		Stevenson et al., 2009		*				*			*		
169		Su et al., 2005		*			*						*
170		Suri et al., 2013		*			*				*		

No	Condition	Author, Year	Type of experiment				Source of cells				Location of the cells		
			In vitro	In vivo	In utero	Ex vivo	Rat	Mouse	Human	Other mammals (e.g., Guinea pigs or Mongolian Gerbils)	Hippocampus /Subgranular zone/Dentate gyrus	Subventricular / periventricular zone	Other regions (e.g., Striato-pallidum complex, mesenchepalon, spinal cord, hypothalamus)
171		Thau-Zuchman et al., 2012		*				*					*
172		Van bokhoven et al., 2011		*			*				*		
173		Vitale et al., 2017		*			*				*		
174		Wang et al., 2005		*			*					*	
175		Wang et al., 2013		*			*				*		
176		Wu et al., 2008		*			*				*		
177		Xie et al., 2015		*			*						*
178		Xu et al., 2017		*			*					*	
179		Xu et al., 2018		*				*			*		
180		Zhang et al., 2006		*			*					*	
181		Zhang et al., 2012		*				*			*		
182		Zhang et al.. 2002		*			*				*		
183		Zheng et al., 2009		*			*				*		
184		Zhu et al. 2017		*				*			*		
185	Modified	Anacker et al., 2013	*						*		*		
186		Borsini et al., 2017	*						*		*		
187		Cheng et al., 2015		*				*			*		
188		Clark et al., 2006		*				*			*		
189		Conti et al., 2017		*				*			*		
190		Ding, et al. 2009	*					*			*		
191		Diniz et al., 2013		*			*				*		
192		Encinas et al., 2006		*				*			*		
193		Esmaili et al., 2016	*					*					*
194		Fenton et al., 2015		*			*				*		
195		Hicks et al., 2012		*			*				*		
196		Ishizuka et al., 2012	*					*					*
197		Kanemura et al., 2005	*						*				*

No	Condition	Author, Year	Type of experiment				Source of cells				Location of the cells		
			In vitro	In vivo	In utero	Ex vivo	Rat	Mouse	Human	Other mammals (e.g., Guinea pigs or Mongolian Gerbils)	Hippocampus /Subgranular zone/Dentate gyrus	Subventricular / periventricular zone	Other regions (e.g., Striato-pallidum complex, mesenchepalon, spinal cord, hypothalamus)
198		Kitamura et al., 2011		*			*				*		
199		Lee et al., 2016	*						*				*
200		Liu et al., 2018		*				*			*		
201		Nautiyal et al., 2012		*				*			*		
202		Rainer et al., 2012		*				*			*		
203		Raman et al., 2013		*				*			*		
204		Sargeant et al., 2008			*			*					*
205		Sawada et al., 2018		*				*				*	
206		Siopi et al., 2016		*				*			*		
207		Surget et al., 2016		*				*			*		
208		Tikhinova et al., 2017		*			*				*		
209		Wong et al., 2005		*			*				*		
210		Yanpallewar et al., 2010	*				*				*		
211		Yoo et al., 2014		*				*			*		
212		Zhang et al., 2014	*				*						*
213		Zhang et al., 2016		*				*			*		
214		Zhao et al., 2015		*				*			*		
215		Zhou et al., 2016		*				*			*		

Supplemental Table 4. Distribution of the Drug Classes Based on the Effect on Neuronal Stem Cells under Physiologic Conditions. The number of publications reporting a stimulating, inhibiting or neutral effect on neuronal stem cell proliferation or differentiation is given. Relative percentages per drug class are indicated in brackets.

Drug classes	Proliferation			Differentiation		
	Stimulating	Neutral	Inhibiting	Stimulating	Neutral	Inhibiting
Analgesic	2 (14.3%)	2 (14.3%)	10 (71.4%)	5 (26.3%)	2 (10.5%)	12 (63.2%)
Antibiotic	5 (35.7%)	3 (21.4%)	6 (42.9%)	3 (20%)	6 (40%)	6 (40%)
Antidepressant	21 (56.7%)	11 (29.8%)	5 (13.5%)	16 (51.6%)	11 (35.5%)	4 (12.9%)
Antidiabetic	2 (50%)	1 (25%)	1 (25%)	4 (50%)	2 (25%)	2 (25%)
Antihypertensive	4 (57.1%)	3 (42.9%)	0	5 (45.5%)	2 (18.2%)	4(36.3%)

Supplemental Table 5. Distribution of the Drug Subclasses Based on the Effect on Neuronal Stem Cells. The number of publications reporting stimulating, inhibiting or neutral effects on stem cell proliferation or differentiation is given. *COX2: cyclooxygenase-2; NSAID: nonsteroidal anti-inflammatory drug; MAO: monoamine oxidase; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor.*

Drug classes	Drug subclasses	Proliferation				Differentiation		
		Stimulating	Neutral	Inhibiting		Stimulating	Neutral	Inhibiting
Analgesic	COX2 Inhibitor	3	2	5		0	0	1
	NSAID	3	0	3		0	1	2
	Opioid	0	3	12		6	1	10
Antibiotic	Aminoglycoside	0	2	6		0	2	6
	Macrolide	2	2	3		2	2	4
	Quinolone	4	0	0		2	1	0
	Tetracycline	2	1	1		2	2	2
Antidepressant	MAO Inhibitor	0	1	2		1	2	3
	SNRI	0	0	0		1	0	1
	SSRI	27	11	4		16	10	5
	Tricyclic Antidepressant	12	3	0		12	1	1
Antidiabetic	Incretin mimetic	1	0	0		2	0	0
	Insulin	2	2	1		4	2	2
	Non sulfonylurea	0	0	0		1	0	0

	Thiazolidinediones	0	1	1	2	2	4
Antihypertensive	Aldosterone receptor inhibitor	1	1	1	1	0	0
	Alpha blocker	3	0	0	1	0	0
	Beta bloker	1	0	0	1	1	0
	Calcium channel blocker	0	1	0	2	1	2
	Loop diuretic	2	1	0	2	0	0

Supplemental Table 6. Characteristics of the Publications Included in the Meta-Analysis on Proliferation under Physiologic Conditions. *BrdU: bromodeoxyuridine; SSRI: selective serotonin reuptake inhibitor; ICR: Institute of cancer research (origin of the mouse strain); NeuN: neuronal nuclei; MAO: monoamine oxidase*

Author	Year	PMID	Journal	Impact factor	Type of experiment	Source of the sample	Result	Sub-class of drugs	Drug	Statistical analysis	P value	Mechanism	Control group	Blind experiment	Outlier	Technical (TR)/ biological replicate (BR)
Alves et al.	2017	28291258	Translational Psychiatry	4.691	In vivo	Dorsal dentate gyrus of male Wistar Han rats	Positive (BrdU): Fluoxetine Neutral (BrdU): Imipramine	SSRI and tricyclic antidepressant	Fluoxetine and Imipramine	Student t test	P<0.05	Proposed	Yes	No	NA	BR
Brooker et al.	2017	27698430	Neuropharmacology	4.249	In vivo	Dentate gyrus of C57BL/6 male and female mice	Positive (BrdU)	SSRI	Fluoxetine	Unpaired t test	P<0.05	Proven	Yes	Yes	NA	BR
Cowen et al.	2008	18616933	Brain Research	2.494	In vivo	Dentate gyrus of male Sprague Dawley rats	Neutral (Ki67 and BrdU)	SSRI	Fluoxetine	Two way ANOVA	p<0.05	NA	Yes	Yes	NA	BR
Hanson et al.	2011	21220416	Journal of pharmacology and experimental therapeutics	3.828	In vivo	Dentate gyrus of adult male Sprague Dawley rats	Neutral (BrdU)	SSRI	Fluoxetine	Two way ANOVA	p<0.001	Proposed	Yes	Yes	NA	BR
Holick et al.	2008	17429410	Neuropsychopharmacology	3.661	In vivo	Dentate gyrus of BALB7cJ male mice	Neutral (BrdU)	SSRI	Fluoxetine	ANOVA with Newman-Keuls	p<0.05	Proposed	Yes	No	NA	BR
Hui et al.	2014	25522429	International Journal of Neuropsychopharmacology	4.009	In vitro	Hippocampal neural progenitor cells of fetal Sprague Dawley rats	Positive (BrdU)	SSRI	Fluoxetine	ANOVA	p<0.01	Proven	Yes	No	NA	TR

Author	Year	PMID	Journal	Impact factor	Type of experiment	Source of the sample	Result	Sub-class of drugs	Drug	Statistical analysis	P value	Mechanism	Control group	Blind experiment	Outlier	Technical (TR)/ biological replicate (BR)
Kodama et al.	2004	15476686	Biological Psychiatry	6.159	In vivo	Hippocampal, prelimbic. striatum of male Sprague Dawley rats	Positive (BrdU)	SSRI	Fluoxetine	ANOVA	P<0.05	Proposed	Yes	Yes	NA	BR
Kohl et al.	2012	22211740	European Journal of Neuroscience	3.753	In vivo	Hippocampus of male and female C57/BL6 mice	Positive (BrdU)	SSRI	Fluoxetine	Two way ANOVA with Bonferroni posthoc	p<0.05	Proven	Yes	Yes	NA	BR
Lee et al.	2009	19819298	Neuroscience Letter	1.925	In vivo	Hippocampus of male ICR mice	Positive (BrdU)	Tricyclic antidepressant	Imipramine	ANOVA with Student-Newman - Keuls posthoc	p<0.05	Proposed	Yes	No	NA	BR
Marlatt et al.	2010	20381469	Brain Research	2.623	In vivo	Dentate gyrus of female C57BL6 mice	Positive (BrdU/ NeuN)	SSRI	Fluoxetine	One way ANOVA	p<0.003	Proposed	Yes	No	NA	BR
Meyer et al.	2017	27569185	Behavioural Brain Research	3.173	In vivo	Subgranular zone and subventricular zone of male Babl/C mice	Positive (BrdU)	Tricyclic antidepressant	Imipramine	One way ANOVA	p<0.01	Proposed	Yes	Yes	NA	BR
Nackenoff et al.	2017	28272863	ACS Chemical Neuroscience	4.211	In vivo	Hippocampus of male C57BL/6 mice	Positive (BrdU)	SSRI	Vortioxetine & Paroxetine	ANOVA and horn sidak post hoc	p<0.05	Proposed	Yes	Yes	NA	BR
Nasrallah et al.	2010	20682307	Brain Research	2.623	In vivo	Dentate gyrus and subventricular zone of male Sprague Dawley rats	Positive (BrdU): Paliperidone Neutral (BrdU): Fluoxetine and Risperidone	SSRI	Paliperidone Fluoxetine Risperidone	One way ANOVA	p<0.05	NA	Yes	Yes	NA	BR

Author	Year	PMID	Journal	Impact factor	Type of experiment	Source of the sample	Result	Sub-class of drugs	Drug	Statistical analysis	P value	Mechanism	Control group	Blind experiment	Outlier	Technical (TR)/ biological replicate (BR)
Ohira et al.	2011	21385396	Molecular Brain	NA	In vivo	Dentate gyrus of male C57BL6 mice	Positive (BrdU and Ki67)	SSRI	Fluoxetine	One way ANOVA with Scheffe posthoc	p<0.01	Proposed	Yes	No	NA	BR
Pechnick et al.	2011	22076148	PLoS One	4.092	In vivo	Subgranular zone of male C57BL6 mice	Positive (BrdU)	Tricyclic Antidepressant	Imipramine	Two way ANOVA with Newman-Keuls posthoc	p<0.05	Proven	Yes	Yes	NA	BR
Petit et al.	2013	23573275	PLoS One	3.534	In vivo	Granule cells of the olfactory bulb of male and female C56/BL7 mice	Neutral (BrdU)	MAO Inhibitor	Rasagiline	One way ANOVA	NA	NA	Yes	Yes	NA	BR
Rayen et al.	2011	21912658	PLoS One	4.092	In utero	Dentate gyrus of Sprague Dawley rat pups	Negative (Ki67)	SSRI	Fluoxetine	ANOVA	p<0.05	Proposed	Yes	No	NA	BR
Santarelli et al.	2003	12907793	Science	29.162	In vivo	Hippocampus of female and male 129/sv mice	Positive (BrdU)	SSRI	Fluoxetine	ANOVA with Fischer posthoc	p<0.01	Proven	Yes	No	NA	BR
Schiavon et al.	2016	26187374	Progress in neuro-psychopharmacology & biological psychiatry	4.187	In vivo	Subventricular zone and subgranular zone of male Swiss Albino mice	Positive (BrdU)	Tricyclic Antidepressant	Imipramine	One way ANOVA	p<0.001	Proposed	Yes	No	NA	BR
Sun et al.	2010	20123967	Molecular and Cellular Biology	6.188	In vitro	Neural stem cells from (unspecified strain and	Negative (BrdU)	MAO Inhibitor	Pargyline * Tranylcypromine**	Student-t-test	*p<0.001 **p<0.01	Proven	Yes	No	NA	TR

Author	Year	PMID	Journal	Impact factor	Type of experiment	Source of the sample	Result	Sub-class of drugs	Drug	Statistical analysis	P value	Mechanism	Control group	Blind experiment	Outlier	Technical (TR)/ biological replicate (BR)
						sex) mouse brain										
Yu et al.	2017	28045461	Translational Psychiatry	4.691	In vivo	Subgranular zone of male Wistar dams rats	Neutral (Ki67)	SSRI	Fluoxetine	Two way ANOVA	$p<0.05$	Proposed	Yes	Yes	NA	BR

Supplemental Table 7. Characteristics of the Publications Included in the Meta-Analysis on Differentiation under Physiologic Conditions. *SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; DCX: doublecortin.*

Author	Year	PMID	Journal	Impact Factor	Type of experiment	Source of the sample	Result	Sub-class of drugs	Drug	Statistical analysis	P value	Mechanism	Control group	Blind experiment	Outlier	Technnical (TR)/ biological replicate (BR)
Asokan et al.	2014	24896246	PLoS One	3.234	In vivo	Dentate gyrus of male Long Evans rats	Negative (DCX)	SNRI	Desvenlafaxine	One way ANOVA with Duncan post hoc	p<0.05	Proposed	Yes	No	NA	BR
Gemmel et al.	2017	28735226	Psychoneuroendocrinology	4.731	In vivo	Granule cells of female Spraque Dawleys rats	Neutral (DCX)	SSRI	Fluoxetine	ANOVA	p<0.05	Proposed	Yes	Yes	NA	BR
Gemmel et al.	2018	29203333	Behavioural Brain Research	3.173	In vivo	Dorsal hippocampus of female Spraque Dawleys rats	Positive (DCX)	SSRI	Fluoxetine	ANOVA	p<0.05	Proposed	Yes	No	NA	BR
Holick et al.	2008	17429410	Neuropsychopharmacology	6.835	In vivo	Dentate gyrus of male Balb/cJ mice	Neutral (DCX)	SSRI	Fluoxetine	ANOVA with Neuman-Keuls Post hoc	p<0.05	Proposed	Yes	No	NA	BR
Meyer et al.	2017	27569185	Behavioural Brain Research	3.173	In vivo	Subgranular zone and subventricular zone of male Babl/C mice	Positive (DCX)	Tricyclic antidepressant	Imipramine	One way ANOVA	p<0.001	Proposed	Yes	Yes	NA	BR
Olesen et al.	2017	28461249	Neurobiology of Disease	5.227	In vivo	Granule cells of male B6C3 hybrid rats	Neutral (DCX)	SSRI	Paroxetine	ANOVA with Tukey post hoc	p<0.05	Proposed	Yes	No	NA	BR
Pechnick et al.	2011	22076148	PLoS One	4.092	In vivo	Subgranular zone of male C57BL6 mice	Positive (DCX)	Tricyclic Antidepressant	Imipramine	Two way ANOVA with Neuman-Keuls Post hoc	p<0.05	Proven	Yes	Yes	NA	BR
Rayen et al.	2011	21912658	PLoS One	4.092	In utero	Dentate gyrus of Sprague Dawley rat pups	Nutral (DCX))	SSRI	Fluoxetine	ANOVA	p<0.05	Proposed	Yes	No	NA	BR

Supplemental Table 8. Characteristics of the Publications Included in the Meta-Analysis on Proliferation in the Depression Condition. *SSRI: selective serotonin reuptake inhibitor; BrdU: bromodeoxyuridine*

Author	Year	PMID	Journal	Impact Factor	Type of experiment	Source of the sample	Result	Sub-class of drugs	Drug	Statistical analysis	P value	Mechanism	Control group	Blind experiment	Outlier	Technnical (TR)/ biological replicate (BR)
Alboni et al.	2017	26645631	Molecular Psychiatry	11.64	In vivo	Hippocampus of C57BL/6 mice	Negative (Ki67)	SSRI	Fluoxetine	One way ANOVA	p<0.05	Proven	Yes	No	NA	BR
Christensen et al.	2012	22406239	European Neuropsychopharmacology	4.595	In vivo	Dentate gyrus of rats	Neutral (BrdU)	SSRI	Gaboxadol	Student t test	p<0.05	Proposed	Yes	No	NA	BR
Jayakumar et al.	2017	28764145	Journal of Clinical and Diagnostic Research	NA	In vivo	Hippocampus of male Wistar albino rats	Positive (BrdU)	SSRI	Fluoxetine	ANOVA with Tukey Post hoc	p<0.05	Proposed	Yes	No	NA	BR
Kuipers et al.	2013	23994757	Neuropharmacology	4.819	In vivo	Hippocampus of male and female Wistar rats	Positive (BrdU)	Tricyclic antidepressant	Tianeptine	ANOVA	p<0.05	Proposed	Yes	Yes	NA	BR
Petersen et al.	2009	19135130	Neuroscience letters	1.925	In vivo	Hippocampus of female Flinders sensistive Line rats	Neutral (BrdU)	Tricyclic antidepressant	Nortryptiline	Student t test	P<0.05	proposed	Yes	No	NA	BR
Vitale et al.	2017	28417659	Psychopharmacology	3.222	In vivo	Hippocampus of male Wistar rats	Positive (BrdU)	SSRI	Fluoxetine	ANOVA with student-Newman-Keuls post hoc	p<0.05	Proposed	Yes	Yes	NA	BR

Example for the manual calculation for meta-analysis. Data used for calculation from Sun et al., 2010 (Subgroup MAO Inhibitor, Figure 2). The Excel sheet for all calculations is provided in Supplemental xls.

1. **Data needed are the mean, SD, and N in each group:**

n treat	n control	SD treat	SD control	mean treat	mean control
4	4	2.12	5.14	13.92	47.11

2. RawDiff and pooled standard deviation:

RawDiff = Mean treatment – Mean control
SDpooled = Sqr((((N1 - 1) * SD1 ^ 2 + (N2 - 1) * SD2 ^ 2) / (N1 + N2 - 2)))
** Option for pooled variance **
RawDiffSE = Sqr(SD1^2 / N1 + SD2^2 / N2)

RawDiff = 13,92 - 47,11= - 33.19
SD_{pooled} = Sqr((((4 - 1) * 2.12 ^ 2 + (4 - 1) * 5,14 ^ 2) / (4 + 4 - 2))) = 3.932
** Option for pooled variance **
RawDiffSE = Sqr((2.12)^2 / 4 + (5,14)^2 / 4) = 2.78

3. Standardized mean difference:

StdDiff = RawDiff / SDpooled
StdDiffSE = Sqr(1 / N1 + 1 / N2 + StdDiff ^ 2 / (2 * (N1 + N2)))

StdDiff = -33,19 / 3.931= -8.442
StdDiffSE = Sqr(1 / 4 + 1 / 4 + 1,014 ^ 2 / (2 * (4 + 4))) = 2.226

4. Hedge's g, SE(g), Variance(g), lower and upper 95%CI:

Hedge's g = (mean treat-mean control/SDpooled)*(1-(3/(4*N-9))
SE(g) = Sqr((N/(ntreat*ncontrol)+(SMD(Hedge's g)/2(N-3.94)))
Where N is the sum of ntreat and ncontrol.
Variance(g) = SE(g)^2
LL for 95% CI = Hedge's g - (1.96*SE(g))
UL for 95% CI = Hedge's g + (1.96*SE(g))

Hedge's g = (13.92-47.11/ 3.931)*(1-(3/(4*8-9)) = -7.341
SE(g) = Sqr ((8/(4.4)+(- 7.340858)/2(8-3.94)))= 2.671
Variance(g) = 2.671^2 = 7.136
LL for 95% CI = -7.341 - (1.96*2.671) = -12.577
UL for 95% CI = -7.341 + (1.96*2.671) = -2.105

5. Weight, g*W, g^2*W, W^2

Weight = W = 1/SE(g)^2 = 1/Var(g)

W = 1/2.671^2 = 1/7.136 = 0.140
g*W = -7.341*0.140 = -1.209

g^2*W = -7.341^2 *0.140 = 7.551
W^2 = 0.140^2 = 0.020

6. Chi^2, C, Tau^2, I^2

Chi^2 = Sum(g^2*W) – ((Sum(g*W)^2)/(Sum(W)) p = CHIVERT(Chi^2;df) C = Sum(W)-(Sum(W^2)/Sum(W)) Tau^2 = (Chi^2 – df)/C I^2 = (Chi^2 – df)/Chi^2 *100 With df as the number of studies minus 1.

Chi^2 = 98.990 – (30.337^2/67.821) = 85.420
p = CHIVERT(85.420;26) = 2.989*10E-8
C = 67.821 – 245.196/67.821 = 64.205
Tau^2 = (85.420 – 26)/64.205 = 0.925
I^2 = (85.420 – 26)/85.420 = 69.562

7. Weight adjusted for random effects, %Wran, g*Wran, g^2*Wran, Wran^2

Wran = 1/(SE(g)^2+Tau^2) = 1/(Var(g) + Tau^2)

Wran = 1/(2.671^2+0.925) = 1/(7.136 +0.925) = 0.124
%Wran = 0.124/18.047 * 100% = 0.7%
g*Wran = -7.341*0.124 = -0.911
g^2*Wran = -7.341^2*0.124 = 6.684
Wran^2 = 0.124^2 = 0.015

8. Random-effect overall effect size (ES), overall ES variance and SE, LL and UL for 95% CI

Random-effect overall ES = Sum(g*Wran)/Sum(Wran) Variance(overall ES) = 1/Sum(Wran) SE(overall ES) = Sqr(1/Sum(Wran)) LL for 95% CI = overall ES - (1.96*SE(overall ES)) UL for 95% CI = overall ES + (1.96*SE(overall ES)) Z = overall ES/SE(overall ES) p(Z, 2-tailed) = 2 * NORMSDIST(Z) or check Z-table

Overall ES = 11.958/18.047 = 0.663
Variance(overall ES) = 0.055
SE(overall ES) = 0.235
LL for 95% CI = 0.201
UL for 95% CI = 1.124
Z = 0.663/0.235 = 2.815
p = 0.005

PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5-6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplemental Data
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6-7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6-7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6-7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6-7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	13-14
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8, Figure 1, Supplemental Table 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8-10, Table 1-2, Supplemental Tables 2-5
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	12-13
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure 2-3, Table 1-2, Supplemental Tables 2, 3, 6-8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9-10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10, 13-14
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10-11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13-14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	15

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097 For more information, visit: **www.prisma-statement.org**.

Supplemental References

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Supporting Figure 2. Forest Plot of the Effect of Antidepressants under Physiologic Conditions

Proliferation - Overall effect

		n treat	n control	SD treat
SSRI	Alves et al., 2017	4	4	14.73
	Brooker et al., 2017	4	4	2568
	Cowen et al., 2008	8	8	1470.78
	Hanson et al., 2011	12	12	602.75
	Holick et al., 2008	5	6	498.01
	Hui et al., 2014	5	5	17
	Kodama et al., 2004	10	11	1001.6
	Kohl et al., 2012	9	9	954
	Marlatt et al., 2010	6	6	249.84
	Nackennoff et al., 2017	4	4	102.01
	Nackennoff et al., 2017	4	4	141.2
	Nasrallah et al., 2010	7	7	4246
	Ohira et al., 2011	8	8	3.88
	Olesen et al., 2017	15	17	1.08
	Pechnick et al., 2011	5	5	303.89
	Rayen et al., 2011	5	5	1470.23
	Santarelli et al., 2003	7	7	1254.22
	Yu et al., 2017	8	8	39.3
Tricyclic antidepressants	Alves et al., 2017	4	4	5.86
	Kuipers et al., 2013	6	6	174.57
	Lee et al., 2009	4	4	12.81
	Meyer et al., 2017	6	6	2.5
	Pechnick et al., 2011	5	5	50.51
	Pechnick et al., 2011	5	5	143.7
	Schiavon et al., 2016	8	9	15.36
MAO inhibitor	Petit et al., 2013	4	6	2950.8
	Sun et al., 2010	4	4	2.12
	Sums			

Proliferation - Subgroup analyses

		n treat	n control	SD treat
SSRI	Alves et al., 2017	4	4	14.73
	Brooker et al., 2017	4	4	2568
	Cowen et al., 2008	8	8	1470.78
	Hanson et al., 2011	12	12	602.75
	Holick et al., 2008	5	6	498.01
	Hui et al., 2014	5	5	17
	Kodama et al., 2004	10	11	1001.6
	Kohl et al., 2012	9	9	954
	Marlatt et al., 2010	6	6	249.84
	Nackennoff et al., 2017	4	4	102.01
	Nackennoff et al., 2017	4	4	141.2
	Nasrallah et al., 2010	7	7	4246
	Ohira et al., 2011	8	8	3.88
	Olesen et al., 2017	15	17	1.08

	Pechnick et al., 2011	5	5	303.89
	Rayen et al., 2011	5	5	1470.23
	Santarelli et al., 2003	7	7	1254.22
	Yu et al., 2017	8	8	39.3
	Sums			
Tricyclic antidepressants	Alves et al., 2017	4	4	5.86
	Kuipers et al., 2013	6	6	174.57
	Lee et al., 2009	4	4	12.81
	Meyer et al., 2017	6	6	2.5
	Pechnick et al., 2011	5	5	50.51
	Pechnick et al., 2011	5	5	143.7
	Schiavon et al., 2016	8	9	15.36
	Sums			
MAOI	Petit et al., 2013	4	6	2950.8
	Sun et al., 2010	4	4	2.12
	Sums			

Differentiation - Overall effect

		n treat	n control	SD treat
	Asokan et al., 2014	5	5	11.18
	Gemmel et al., 2017	12	12	167.19
	Gemmel et al., 2018	9	10	660.1
	Holick et al., 2008	5	6	398.09
	Meyer et al., 2017	7	7	11.07
	Olesen et al., 2017	15	17	928.79
	Pechnick et al., 2011	5	5	76.45
	Rayen et al., 2011	5	5	22101.12
	Sums			

Supporting Figure 3. Forest Plot of the Effect of Antidepressants in Models of Depression

Proliferation - Overall effect

		n treat	n control	SD treat
	Alboni et al., 2017	11	10	12.78
	Christensen et al., 2012	8	16	306.01
	Jayakumar et al., 2017	6	6	19.84
	Kuipers et al., 2013	6	6	311.19
	Petersen et al., 2009	12	12	218.99
	Vitale et al., 2017	8	8	65.38
	Sums			

lculations meta-analysis

SD control	mean treat	mean control	N	Raw difference	SD pooled
16.46	55.97	40.14	8	15.83	15.619
2598	11472	6948	8	4524	2583.044
1745.13	13103	13401	16	-298	1613.796
599.28	1967	1983	24	-16	601.018
324.03	762.38	952.92	11	-190.54	410.560
3.21	70.4	56.4	10	14	12.233
948.48	8340	6910	21	1430	974.003
108	1787	879	18	908	678.889
170.75	985	902	12	83	213.981
45.76	1741.71	976.82	8	764.89	79.057
45.76	2145	976.82	8	1168.18	104.956
5320	19443	17403	14	2040	4813.051
1.9	15.24	8.24	16	7	3.055
2.18	1.74	2.81	32	-1.07	1.755
127.78	1328.57	657.14	10	671.43	233.106
2329.32	7320	9487.2	10	-2167.2	1947.730
561.05	3375	1312.5	14	2062.5	971.557
30.59	90.32	100	16	-9.68	35.215
16.46	36.95	40.14	8	-3.19	12.355
99.5	2699.02	2798.5	12	-99.48	142.083
14.96	213.52	167.08	8	46.44	13.927
4.09	10.91	11.2	12	-0.29	3.390
127.78	875.14	657.14	10	218	97.157
127.78	842.88	657.14	10	185.74	135.973
7.34	45.98	25.15	17	20.83	11.783
4818.64	29509.97	29508.97	10	1	4216.309
5.14	13.92	47.11	8	-33.19	3.932
				11342.2	19929.530

SD control	mean treat	mean control	N	mean difference	SD pooled
16.46	55.97	40.14	8	15.83	15.619
2598	11472	6948	8	4524	2583.044
1745.13	13103	13401	16	-298	1613.796
599.28	1967	1983	24	-16	601.018
324.03	762.38	952.92	11	-190.54	410.560
3.21	70.4	56.4	10	14	12.233
948.48	8340	6910	21	1430	974.003
108	1787	879	18	908	678.889
170.75	985	902	12	83	213.981
45.76	1741.71	976.82	8	764.89	79.057
45.76	2145	976.82	8	1168.18	104.956
5320	19443	17403	14	2040	4813.051
1.9	15.24	8.24	16	7	3.055
2.18	1.74	2.81	32	-1.07	1.755

127.78	1328.57	657.14	10	671.43	233.106
2329.32	7320	9487.2	10	-2167.2	1947.730
561.05	3375	1312.5	14	2062.5	971.557
30.59	90.32	100	16	-9.68	35.215
				11006.34	15292.623

16.46	36.95	40.14	8	-3.19	12.355
99.5	2699.02	2798.5	12	-99.48	142.083
14.96	213.52	167.08	8	46.44	13.927
4.09	10.91	11.2	12	-0.29	3.390
127.78	875.14	657.14	10	218	97.157
127.78	842.88	657.14	10	185.74	135.973
7.34	45.98	25.15	17	20.83	11.783
				368.05	416.666

4818.64	29509.97	29508.97	10	1	4216.309
5.14	13.92	47.11	8	-33.19	3.932
				-32.19	4220.241

SD control	mean treat	mean control	N	mean difference	SD pooled
4.47	15.5	62.8	10	-47.3	8.514
119.99	299.38	293.19	24	6.19	145.516
522.12	2528.81	1719.89	19	808.92	591.078
264.98	5233.48	5719.62	11	-486.14	330.820
7.41	109.34	87.84	14	21.5	9.419
2111.16	427.82	2.81	32	425.01	1667.224
43.26	393.16	252.13	10	141.03	62.113
3287.54	54386.4	59200.8	10	-4814.4	15799.801
				-3945.19	18614.485

SD control	mean treat	mean control	N	mean difference	SD pooled
11.52	88.14	100	21	-11.86	12.199
613.21	5814.21	5469.94	24	344.27	534.955
19.84	143.1	78.4	12	64.7	19.840
87.06	3059.69	2450.24	12	609.45	228.494
232.19	570.02	566.75	24	3.27	225.687
154.09	662.36	326.88	16	335.48	118.360
				1345.31	1139.535

Raw diff SE	StdDiff d	SE(d)	Hedge's g	SE(g)	Variance(g)
11.044	1.014	0.751	0.881	0.772	0.596
1826.488	1.751	0.832	1.523	0.886	0.786
806.898	-0.185	0.501	-0.175	0.501	0.251
245.364	-0.027	0.408	-0.026	0.408	0.167
259.041	-0.464	0.614	-0.424	0.616	0.379
7.737	1.144	0.682	1.034	0.699	0.488
426.736	1.468	0.492	1.409	0.499	0.249
320.031	1.337	0.521	1.274	0.529	0.280
123.542	0.388	0.583	0.358	0.584	0.341
55.902	9.675	2.520	8.413	3.036	9.217
74.215	11.130	2.871	9.678	3.469	12.036
2572.684	0.424	0.540	0.397	0.542	0.294
1.527	2.291	0.643	2.166	0.667	0.445
0.598	-0.610	0.362	-0.594	0.363	0.132
147.429	2.880	0.903	2.602	0.979	0.958
1231.853	-1.113	0.680	-1.005	0.695	0.483
519.319	2.123	0.668	1.987	0.694	0.482
17.608	-0.275	0.502	-0.260	0.503	0.253
8.736	-0.258	0.710	-0.225	0.711	0.506
82.031	-0.700	0.595	-0.646	0.599	0.359
9.848	3.335	1.093	2.900	1.239	1.535
1.957	-0.086	0.578	-0.079	0.578	0.334
61.448	2.244	0.807	2.027	0.860	0.739
85.997	1.366	0.702	1.234	0.725	0.526
5.956	1.768	0.573	1.678	0.586	0.344
2459.001	0.000	0.645	0.000	0.645	0.417
2.780	-8.442	2.226	-7.341	2.671	7.136
11365.769	32.181	23.004	28.787	25.058	39.733

Raw diff SE	d	Variance(d)	Hedge g	SE(g)	Variance(g)
11.044	1.014	0.751	0.881	0.772	0.596
1826.488	1.751	0.832	1.523	0.886	0.786
806.898	-0.185	0.501	-0.175	0.501	0.251
245.364	-0.027	0.408	-0.026	0.408	0.167
259.041	-0.464	0.614	-0.424	0.616	0.379
7.737	1.144	0.682	1.034	0.699	0.488
426.736	1.468	0.492	1.409	0.499	0.249
320.031	1.337	0.521	1.274	0.529	0.280
123.542	0.388	0.583	0.358	0.584	0.341
55.902	9.675	2.520	8.413	3.036	9.217
74.215	11.130	2.871	9.678	3.469	12.036
2572.684	0.424	0.540	0.397	0.542	0.294
1.527	2.291	0.643	2.166	0.667	0.445
0.598	-0.610	0.362	-0.594	0.363	0.132

147.429	2.880	0.903	2.602	0.979	0.958
1231.853	-1.113	0.680	-1.005	0.695	0.483
519.319	2.123	0.668	1.987	0.694	0.482
17.608	-0.275	0.502	-0.260	0.503	0.253
8648.015	32.954	15.075	29.239	16.443	27.837
8.736	-0.258	0.710	-0.225	0.711	0.506
82.031	-0.700	0.595	-0.646	0.599	0.359
9.848	3.335	1.093	2.900	1.239	1.535
1.957	-0.086	0.578	-0.079	0.578	0.334
61.448	2.244	0.807	2.027	0.860	0.739
85.997	1.366	0.702	1.234	0.725	0.526
5.956	1.768	0.573	1.678	0.586	0.344
255.973	7.668	5.058	6.888	5.299	4.343
2459.001	0.000	0.645	0.000	0.645	0.417
2.780	-8.442	2.226	-7.341	2.671	7.136
2461.781	-8.442	2.871	-7.341	3.317	7.553

Raw diff SE	d	Variance(d)	Hedge g	SE(g)	Variance(g)
5.385	-5.556	1.394	-5.018	1.574	2.478
59.407	0.043	0.408	0.041	0.408	0.167
275.092	1.369	0.510	1.307	0.518	0.268
208.321	-1.470	0.682	-1.344	0.703	0.495
5.035	2.283	0.687	2.137	0.716	0.513
565.408	0.255	0.356	0.248	0.356	0.127
39.284	2.271	0.811	2.051	0.864	0.747
9992.672	-0.305	0.636	-0.275	0.637	0.406
11150.602	-1.111	5.484	-0.852	5.777	5.199

Raw diff SE	d	Variance(d)	Hedge g	SE(g)	Variance(g)
5.303	-0.972	0.462	-0.933	0.465	0.216
187.635	0.644	0.443	0.621	0.444	0.197
11.455	3.261	0.881	3.010	0.946	0.895
131.921	2.667	0.794	2.462	0.842	0.709
92.136	0.014	0.408	0.014	0.408	0.167
59.180	2.834	0.708	2.680	0.740	0.548
487.630	8.449	3.696	7.854	3.846	2.733

LL for 95% CI	UL for 95% CI	Weight W	g*W	g^2*W	W^2	Wran	%Wran
-0.631	2.394	1.679	1.480	1.304	2.818	0.657	3.6
-0.214	3.260	1.273	1.938	2.952	1.620	0.584	3.2
-1.157	0.808	3.980	-0.695	0.121	15.839	0.850	4.7
-0.826	0.775	5.999	-0.154	0.004	35.993	0.916	5.1
-1.632	0.783	2.636	-1.118	0.475	6.946	0.766	4.2
-0.336	2.403	2.049	2.117	2.189	4.196	0.707	3.9
0.431	2.388	4.014	5.657	7.974	16.112	0.851	4.7
0.237	2.311	3.572	4.551	5.796	12.762	0.830	4.6
-0.787	1.503	2.930	1.049	0.376	8.585	0.789	4.4
2.463	14.364	0.108	0.913	7.680	0.012	0.099	0.5
2.879	16.478	0.083	0.804	7.783	0.007	0.077	0.4
-0.665	1.459	3.407	1.352	0.536	11.606	0.820	4.5
0.860	3.473	2.249	4.873	10.557	5.059	0.730	4.0
-1.306	0.117	7.588	-4.510	2.681	57.578	0.946	5.2
0.683	4.520	1.043	2.714	7.062	1.089	0.531	2.9
-2.368	0.358	2.069	-2.079	2.090	4.281	0.710	3.9
0.627	3.348	2.075	4.123	8.194	4.304	0.710	3.9
-1.245	0.726	3.956	-1.028	0.267	15.648	0.849	4.7
-1.619	1.170	1.975	-0.444	0.100	3.902	0.698	3.9
-1.821	0.528	2.784	-1.799	1.163	7.749	0.778	4.3
0.471	5.328	0.651	1.888	5.476	0.424	0.406	2.3
-1.211	1.053	2.997	-0.237	0.019	8.979	0.794	4.4
0.342	3.711	1.353	2.743	5.559	1.832	0.601	3.3
-0.187	2.655	1.903	2.347	2.896	3.620	0.689	3.8
0.529	2.827	2.908	4.879	8.187	8.455	0.788	4.4
-1.265	1.265	2.400	0.001	0.000	5.760	0.745	4.1
-12.577	-2.105	0.140	-1.029	7.551	0.020	0.124	0.7
		67.821	30.337	98.990	245.196	18.047	

LL for 95% CI	UL for 95% CI	Weight (W)	g*W	g^2*W	W^2	Wv	%Wv
-0.631	2.394	1.679	1.480	1.304	2.818	0.673	5.3
-0.214	3.260	1.273	1.938	2.952	1.620	0.597	4.7
-1.157	0.808	3.980	-0.695	0.121	15.839	0.877	6.9
-0.826	0.775	5.999	-0.154	0.004	35.993	0.947	7.4
-1.632	0.783	2.636	-1.118	0.475	6.946	0.788	6.2
-0.336	2.403	2.049	2.117	2.189	4.196	0.726	5.7
0.431	2.388	4.014	5.657	7.974	16.112	0.878	6.9
0.237	2.311	3.572	4.551	5.796	12.762	0.855	6.7
-0.787	1.503	2.930	1.049	0.376	8.585	0.813	6.4
2.463	14.364	0.108	0.913	7.680	0.012	0.099	0.8
2.879	16.478	0.083	0.804	7.783	0.007	0.077	0.6
-0.665	1.459	3.407	1.352	0.536	11.606	0.845	6.6
0.860	3.473	2.249	4.873	10.557	5.059	0.750	5.9
-1.306	0.117	7.588	-4.510	2.681	57.578	0.979	7.7

0.683	4.520	1.043	2.714	7.062	1.089	0.541	4.2
-2.368	0.358	2.069	-2.079	2.090	4.281	0.729	5.7
0.627	3.348	2.075	4.123	8.194	4.304	0.729	5.7
-1.245	0.726	3.956	-1.028	0.267	15.648	0.876	6.9
		50.710	21.986	68.040	204.456	12.781	100.000
-1.619	1.170	1.975	-0.444	0.100	3.902	0.695	14.7
-1.821	0.528	2.784	-1.799	1.163	7.749	0.774	16.4
0.471	5.328	0.651	1.888	5.476	0.424	0.405	8.6
-1.211	1.053	2.997	-0.237	0.019	8.979	0.789	16.7
0.342	3.711	1.353	2.743	5.559	1.832	0.598	12.6
-0.187	2.655	1.903	2.347	2.896	3.620	0.685	14.5
0.529	2.827	2.908	4.879	8.187	8.455	0.783	16.6
		14.571	9.379	23.399	34.961	4.728	100.000
-1.265	1.265	2.400	0.001	0.000	5.760	0.042	56.2
-12.577	-2.105	0.140	-1.029	7.551	0.020	0.033	43.8
		2.540	-1.028	7.551	5.780	0.075	100.000

LL for 95% CI	UL for 95% CI	Weight (W)	g*W	g^2*W	W^2	Wv	%Wv
-8.103	-1.933	0.404	-2.025	10.163	0.163	0.270	5.8
-0.759	0.841	5.998	0.246	0.010	35.982	0.718	15.4
0.293	2.322	3.733	4.881	6.380	13.939	0.669	14.3
-2.722	0.035	2.022	-2.717	3.650	4.089	0.581	12.4
0.733	3.540	1.951	4.168	8.907	3.805	0.575	12.3
-0.449	0.946	7.899	1.963	0.488	62.402	0.739	15.8
0.357	3.745	1.339	2.745	5.630	1.792	0.507	10.8
-1.524	0.974	2.462	-0.677	0.186	6.059	0.612	13.1
		25.808	8.584	35.415	128.231	4.671	100.000

LL for 95% CI	UL for 95% CI	Weight (W)	g*W	g^2*W	W^2	Wv	%Wv
-1.845	-0.021	4.620	-4.312	4.024	21.347	0.511	18.4
-0.249	1.492	5.073	3.152	1.959	25.735	0.516	18.6
1.156	4.865	1.117	3.362	10.119	1.247	0.379	13.7
0.811	4.113	1.410	3.471	8.545	1.987	0.408	14.7
-0.786	0.814	6.000	0.084	0.001	35.998	0.524	18.9
1.229	4.130	1.826	4.893	13.111	3.333	0.437	15.7
		20.045	10.649	37.760	89.647	2.776	100.000

g*Wran	g^2*Wran	Wran^2	Formulas	
0.579	0.511	0.432		
0.890	1.356	0.342	RawDiff =	Mean trea
-0.148	0.026	0.722	SDpooled =	Sqr((((N1
-0.024	0.001	0.838	RawDiffSE =	Sqr(SD1^2
-0.325	0.138	0.587	StdDiff d =	RawDiff /
0.731	0.756	0.500	StdDiffSE = SE(d) =	Sqr(1 / N1
1.200	1.691	0.725	Hedge's g =	(mean tre
1.057	1.346	0.688	SE(g) =	Sqr((N/(n
0.283	0.101	0.623	Variance(g) =	SE(g)^2
0.830	6.979	0.010	LL for 95% CI	Hedge's g
0.747	7.227	0.006	UL for 95% CI	Hedge's g
0.326	0.129	0.673	Weight W =	1/SE(g)^2
1.581	3.426	0.533	Weight adjusted for random effects = Wran =	1/(SE(g)^2
-0.562	0.334	0.895		
1.381	3.593	0.282		
-0.713	0.717	0.504		
1.412	2.806	0.505		
-0.221	0.057	0.720		
-0.157	0.035	0.488		
-0.503	0.325	0.606		
1.178	3.417	0.165		
-0.063	0.005	0.631		
1.218	2.468	0.361		
0.850	1.049	0.475	**Tau^2 = (Chi^2-df)/C=**	0.925
1.322	2.218	0.621	**Chi^2 = Sum(g^2*W) – ((Sum(g*W)^2)/(Sum(W)) =**	**85.420**
			df = number of studies minus 1 =	26
0.000	0.000	0.555	C = Sum(W)-(Sum(W^2)/Sum(W)) =	64.205
-0.911	6.684	0.015		
11.958	47.394	13.502	**I^2 = (Chi^2-df)/Chi^2 *100 =**	**69.562**

g*Wv	g^2*Wv	Wv^2		
0.594	0.523	0.454		
0.909	1.385	0.356		
-0.153	0.027	0.769		
-0.024	0.001	0.897		
-0.334	0.142	0.621		
0.750	0.776	0.527		
1.238	1.745	0.772		
1.090	1.388	0.732		
0.291	0.104	0.660		
0.832	7.004	0.010		
0.749	7.247	0.006		
0.335	0.133	0.715		
1.624	3.519	0.562		
-0.582	0.346	0.959	**Tau^2 = (Chi^2-df)/C=**	0.889

1.408	3.663	0.293	**Chi^2 = Sum(g^2*W) – ((Sum(g*W)^2)/(Sum(W)) =**	**58.507**
-0.732	0.736	0.531	df = number of studies minus 1 =	17
1.449	2.880	0.532	C = Sum(W)-(Sum(W^2)/Sum(W)) =	46.678
-0.228	0.059	0.767		
9.216	31.678	10.162	**I^2 = (Chi^2-df)/Chi^2 *100 =**	**70.944**

-0.156	0.035	0.482		
-0.500	0.323	0.598		
1.174	3.405	0.164	**Tau^2 = (Chi^2-df)/C=**	0.934
-0.062	0.005	0.623	**Chi^2 = Sum(g^2*W) – ((Sum(g*W)^2)/(Sum(W)) =**	**17.362**
1.212	2.456	0.358	df = number of studies minus 1 =	6
0.846	1.043	0.470	C = Sum(W)-(Sum(W^2)/Sum(W)) =	12.171
1.314	2.204	0.613		
3.827	9.472	3.308	**I^2 = (Chi^2-df)/Chi^2 *100 =**	**65.442**

0.000	0.000	0.002	**Tau^2 = (Chi^2-df)/C=**	23.169
-0.242	1.778	0.001	**Chi^2 = Sum(g^2*W) – ((Sum(g*W)^2)/(Sum(W)) =**	**7.135**
-0.242	1.778	0.003	df = number of studies minus 1 =	1
			C = Sum(W)-(Sum(W^2)/Sum(W)) =	0.265
			I^2 = (Chi^2-df)/Chi^2 *100 =	**85.984**

g*Wv	**g^2*Wv**	**Wv^2**		
-1.355	6.798	0.073		
0.029	0.001	0.515		
0.875	1.144	0.448		
-0.781	1.049	0.338	**Tau^2 = (Chi^2-df)/C=**	1.227
1.229	2.625	0.331	**Chi^2 = Sum(g^2*W) – ((Sum(g*W)^2)/(Sum(W)) =**	**32.560**
0.184	0.046	0.546	df = number of studies minus 1 =	7
1.039	2.131	0.257	C = Sum(W)-(Sum(W^2)/Sum(W)) =	20.839
-0.169	0.046	0.375		
1.052	13.840	2.882	**I^2 = (Chi^2-df)/Chi^2 *100 =**	**78.501**

g*Wv	**g^2*Wv**	**Wv^2**		
-0.477	0.445	0.261		
0.321	0.199	0.266	**Tau^2 = (Chi^2-df)/C=**	1.740
1.142	3.438	0.144	**Chi^2 = Sum(g^2*W) – ((Sum(g*W)^2)/(Sum(W)) =**	**32.103**
1.005	2.474	0.167	df = number of studies minus 1 =	5
0.007	0.000	0.275	C = Sum(W)-(Sum(W^2)/Sum(W)) =	15.573
1.171	3.139	0.191		
3.169	9.695	1.304	**I^2 = (Chi^2-df)/Chi^2 *100 =**	**84.425**

atment – Mean control
- 1) * SD1 ^ 2 + (N2 - 1) * SD2 ^ 2) / (N1 + N2 - 2)))
2 / N1 + SD2^2 / N2)
SDpooled
1 + 1 / N2 + StdDiff ^ 2 / (2 * (N1 + N2)))
eat-mean control/SDpooled)*(1-(3/(4*N-9))
treat*ncontrol)+(SMD(Hedge's g)/2(N-3.94)))

; - (1.96*SE(g))
; + (1.96*SE(g))
! = 1/Var(g)
2+Tau^2) = 1/(Var(g) + Tau^2)

p = CHIVERT(Chi^2;df) = 2.98888E-08

Random-effects overall ES = Sum(g*Wran)/Sum(Wran) =
Variance(overall ES) = 1/Sum(Wran) =
SE (overall ES) = Sqr(1/Sum(Wran)) =
LL for 95% CI = overall ES - (1.96*SE(overall ES)) =
UL for 95% CI = overall ES + (1.96*SE(overall ES)) =
Z = overall ES/SE(overall ES) =
p = 2*normsdist(Z) =

Random-effects overall ES = Sum(g*Wran)/Sum(Wran) =

p = CHIVERT(Chi^2;df) = 1.8492E-06 Variance(overall ES) = 1/Sum(Wran) =
SE (overall ES) = Sqr(1/Sum(Wran)) =
LL for 95% CI = overall ES - (1.96*SE(overall ES)) =
UL for 95% CI = overall ES + (1.96*SE(overall ES)) =
Z = overall ES/SE(overall ES) =
p = 2*normsdist(Z) =

Random-effects overall ES = Sum(g*Wran)/Sum(Wran) =
p = CHIVERT(Chi^2;df) = 0.008040438 Variance(overall ES) = 1/Sum(Wran) =
SE (overall ES) = Sqr(1/Sum(Wran)) =
LL for 95% CI = overall ES - (1.96*SE(overall ES)) =
UL for 95% CI = overall ES + (1.96*SE(overall ES)) =
Z = overall ES/SE(overall ES) =
p = 2*normsdist(Z) =

Random-effects overall ES = Sum(g*Wran)/Sum(Wran) =
p = CHIVERT(Chi^2;df) = 0.007559555 Variance(overall ES) = 1/Sum(Wran) =
SE (overall ES) = Sqr(1/Sum(Wran)) =
LL for 95% CI = overall ES - (1.96*SE(overall ES)) =
UL for 95% CI = overall ES + (1.96*SE(overall ES)) =
Z = overall ES/SE(overall ES) =
p = 2*normsdist(Z) =

Random-effects overall ES = Sum(g*Wran)/Sum(Wran) =
p = CHIVERT(Chi^2;df) = 3.19685E-05 Variance(overall ES) = 1/Sum(Wran) =
SE (overall ES) = Sqr(1/Sum(Wran)) =
LL for 95% CI = overall ES - (1.96*SE(overall ES)) =
UL for 95% CI = overall ES + (1.96*SE(overall ES)) =
Z = overall ES/SE(overall ES) =
p = 2*normsdist(Z) =

Random-effects overall ES = Sum(g*Wran)/Sum(Wran) =
p = CHIVERT(Chi^2;df) = 5.66968E-06 Variance(overall ES) = 1/Sum(Wran) =
SE (overall ES) = Sqr(1/Sum(Wran)) =
LL for 95% CI = overall ES - (1.96*SE(overall ES)) =
UL for 95% CI = overall ES + (1.96*SE(overall ES)) =
Z = overall ES/SE(overall ES) =
p = 2*normsdist(Z) =

0.663
0.055
0.235
0.201
1.124
2.815

#NAME? or check Z-table

0.721

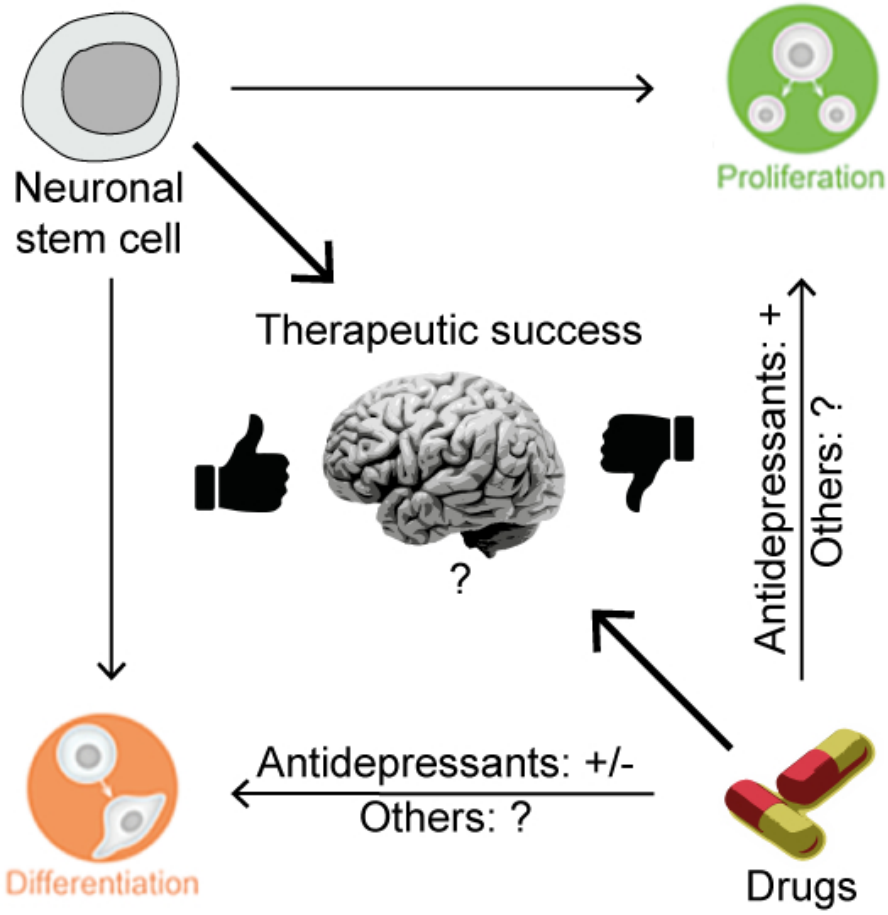
0.078
0.280
0.173
1.269
2.578
#NAME? or check Z-table

0.809
0.211
0.460
-0.092
1.711
1.760
#NAME? or check Z-table

-3.213
13.263
3.642
-10.351
3.925
0.882
#NAME? or check Z-table

0.225
0.214
0.463
-0.682
1.132
0.487
#NAME? or check Z-table

1.142
0.360
0.600
-0.035
2.318
1.902
#NAME? or check Z-table



Our systematic review and meta-analysis revealed that antidepressants and potentially other drugs frequently used in the elderly influence the behavior of neuronal stem cells which may affect the efficacy and safety of stem cell transplantation. We recommend that future research addresses such interactions and investigates the best combination of pharmacological interventions and neuronal stem cell treatments.

50x50mm (300 x 300 DPI)